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(54) Title: ENZYME-BASED GPROTEIN-COUPLED RECEPTOR ASSAY

(57) Abstract: Methods for detecting G-protein coupled receptor (GPCR) activity; methods of assaying GPCR activity; and methods of screening for GPCR ligands, G-protein-coupled receptor kinase (GRK) activity, and compounds that interact with components of the GPRC regulatory process are described.

**TITLE OF THE INVENTION****ENZYME-BASED G PROTEIN-COUPLED RECEPTOR ASSAY**

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**BACKGROUND OF THE INVENTION**

This application claims the benefit from Provisional Application Serial No. 60/180,669, filed February 7, 2000. The entirety of that provisional application is incorporated herein by reference.

10 **Field of the Invention**

This invention relates to methods of detecting G-protein-coupled receptor (GPCR) activity, and provides methods of assaying GPCR activity and methods for screening for GPCR ligands, G-protein-coupled receptor kinase (GRK) activity, and compounds that interact with components of the GPCR regulatory process.

15 The actions of many extracellular signals are mediated by the interaction of G-protein-coupled receptors (GPCRs) and guanine nucleotide-binding regulatory proteins (G-proteins). G-protein-mediated signaling systems have been identified in many divergent organisms, such as mammals and yeast. The GPCRs represent a large super family of proteins which have divergent amino acid sequences, but share common structural features, in particular, the  
20 presence of seven transmembrane helical domains. GPCRs respond to, among other extracellular signals, neurotransmitters, hormones, odorants and light. Individual GPCR types activate a particular signal transduction pathway; at least ten different signal transduction pathways are known to be activated via GPCRs. For example, the beta 2-adrenergic receptor ( $\beta$ 2AR) is a prototype mammalian GPCR. In response to agonist binding,  
25  $\beta$ 2AR receptors activate a G-protein (Gs) which in turn stimulates adenylate cyclase activity and results in increased cyclic adenosine monophosphate (cAMP) production in the cell.

The signaling pathway and final cellular response that result from GPCR stimulation depends on the specific class of G-protein with which the particular receptor is coupled (Hamm, "The many faces of G-Protein Signaling." J. Biol. Chem., 273:669-672 (1998)). For instance, coupling to the Gs class of G-proteins stimulates cAMP production and activation of Protein Kinase A and C pathways, whereas coupling to the Gi class of G-proteins down regulates cAMP. Other second messenger systems as calcium, phospholipase C, and phosphatidylinositol 3 may also be utilized. As a consequence, GPCR signaling events have predominantly been measured via quantification of these second messenger products.

A common feature of GPCR physiology is desensitization and recycling of the receptor through the processes of receptor phosphorylation, endocytosis and dephosphorylation (Ferguson, et al., "G-protein-coupled receptor regulation: role of G-protein-coupled receptor kinases and arrestins." Can. J. Physiol. Pharmacol., 74:1095-1110 (1996)). Ligand-occupied GPCRs can be phosphorylated by two families of serine/threonine kinases, the G-protein-coupled receptor kinases (GRKs) and the second messenger-dependent protein kinases such as protein kinase A and protein kinase C. Phosphorylation by either class of kinases serves to down-regulate the receptor by uncoupling it from its corresponding G-protein. GRK-phosphorylation also serves to down-regulate the receptor by recruitment of a class of proteins known as the arrestins that bind the cytoplasmic domain of the receptor and promote clustering of the receptor into endocytic vesicles. Once the receptor is endocytosed, it will either be degraded in lysosomes or dephosphorylated and recycled back to the plasma membrane as fully-functional receptor.

Binding of an arrestin protein to an activated receptor has been documented as a common phenomenon for a variety of GPCRs ranging from rhodopsin to  $\beta$ 2AR to the

neurotensin receptor (Barak, et al., "A  $\beta$ -arrestin/Green Fluorescent fusion protein biosensor for detecting G-Protein-Coupled Receptor Activation," J. Biol. Chem., 272:27497-500 (1997)). Consequently, monitoring arrestin interaction with a specific GPCR can be utilized as a generic tool for measuring GPCR activation. Similarly, a single G-protein and GRK also partner with a variety of receptors (Hamm, et al. (1998) and Pitcher et al., "G-Protein-Coupled Receptor Kinases," Annu. Rev. Biochem., 67:653-92 (1998)), such that these protein/protein interactions may also be monitored to determine receptor activity.

The present invention involves the use of a proprietary technology (ICAST<sup>TM</sup>, Intercistronic Complementation Analysis Screening Technology) for monitoring protein/protein interactions in GPCR signaling. The method involves using two inactive  $\beta$ -galactosidase mutants, each of which is fused with one of two interacting protein pairs, such as a GPCR and an arrestin. The formation of an active  $\beta$ -galactosidase complex is driven by interaction of the target proteins. In this system,  $\beta$ -galactosidase activity acts as a read out of GPCR activity. FIGURE 23 is a schematic depicting the method of the present invention. FIGURE 23 shows two inactive mutants that become active when they interact. In addition, this technology could be used to monitor GPCR-mediated signaling pathways via other downstream signaling components such as G-proteins, GRKs or c-Src.

Many therapeutic drugs in use today target GPCRs, as they regulate vital physiological responses, including vasodilation, heart rate, bronchodilation, endocrine secretion and gut peristalsis. See, e.g., Lefkowitz et al., Annu. Rev. Biochem., 52:159 (1983). For instance, drugs targeting the highly studied GPCR,  $\beta$ 2AR are used in the treatment of anaphylaxis, shock hypertension, asthma and other conditions. Some of these drugs mimic



the ligand for this receptor. Other drugs act to antagonize the receptor in cases when disease arises from spontaneous activity of the receptor.

Efforts such as the Human Genome Project are identifying new GPCRs ("orphan" receptors) whose physiological roles and ligands are unknown. It is estimated that several thousand GPCRs exist in the human genome. Of the 250 GPCRs identified to date, only 150 have been associated with ligands.

### SUMMARY OF THE INVENTION

A first aspect of the present invention is a method that monitors GPCR function proximally at the site of receptor activation, thus providing more information for drug discovery purposes due to fewer competing mechanisms. Activation of the GPCR is measured by a read-out for interaction of the receptor with a regulatory component such as arrestin, G-protein, GRK or other kinases, the binding of which to the receptor is dependent upon agonist occupation of the receptor. Protein/protein interaction is detected by complementation of reporter proteins such as utilized by the ICAST™ technology.

A further aspect of the present invention is a method of assessing G-protein-coupled receptor (GPCR) pathway activity under test conditions by providing a test cell that expresses a GPCR, e.g., muscarinic, adrenergic, dopamine, angiotensin or endothelin, as a fusion protein to a mutant reporter protein and interacting, i.e., G-proteins, arrestin or GRK, as a fusion protein with a complementing reporter protein. When test cells are exposed to a known agonist to the target GPCR under test conditions, activation of the GPCR will be monitored by complementation of the reporter enzyme. Increased reporter enzyme activity reflects interaction of the GPCR with its interacting protein partner.

A further aspect of the present invention is a method of assessing GPCR pathway activity in the presence of a test kinase.

A further aspect of the present invention is a method of assessing GPCR pathway activity in the presence of a test G-protein.

5 A further aspect of the present invention is a method of assessing GPCR pathway activity upon exposure of the test cell to a test ligand.

A further aspect of the present invention is a method of assessing GPCR pathway activity upon co-expression in the test cell of a second receptor.

A further aspect of the present invention is a method for screening for a ligand or  
10 agonists to an orphan GPCR. The ligand or agonist could be contained in natural or synthetic libraries or mixtures or could be a physical stimulus. A test cell is provided that expresses the orphan GPCR as a fusion protein with one  $\beta$ -galactosidase mutant and, for example, an arrestin or mutant form of arrestin as a fusion protein with another  $\beta$ -galactosidase mutant. The interaction of the arrestin with the orphan GPCR upon receptor activation is measured by  
15 enzymatic activity of the complemented  $\beta$ -galactosidase. The test cell is exposed to a test compound, and an increase in  $\beta$ -galactosidase activity indicates the presence of a ligand or agonist.

A further aspect of the present invention is a method for screening a protein of interest, for example, an arrestin protein (or mutant form of the arrestin protein) for the ability  
20 to bind to a phosphorylated, or activated, GPCR. A cell is provided that expresses a GPCR and contains  $\beta$ -arrestin. The cell is exposed to a known GPCR agonist and then reporter enzyme activity is detected. Increased reporter enzyme activity indicates that the  $\beta$ -arrestin molecule can bind to phosphorylated, or activated, GPCR in the test cell.

A further aspect of the present invention is a method to screen for an agonist to a specific GPCR. The agonist could be contained in natural or synthetic libraries or could be a physical stimulus. A test cell is provided that expresses a GPCR as a fusion protein with one  $\beta$ -galactosidase mutant and, for example, an arrestin as a fusion protein with another  $\beta$ -galactosidase mutant. The interaction of arrestin with the GPCR upon receptor activation is measured by enzymatic activity of the complemented  $\beta$ -galactosidase. The test cell is exposed to a test compound, and an increase in  $\beta$ -galactosidase activity indicates the presence of an agonist. The test cell may express a known GPCR or a variety of known GPCRs, or may express an unknown GPCR or a variety of unknown GPCRs. The GPCR may be, for example, an odorant GPCR or a  $\beta$ AR GPCR.

A further aspect of the present invention is a method of screening a test compound for G-protein-coupled receptor (GPCR) antagonist activity. A test cell is provided that expresses a GPCR as a fusion protein with one  $\beta$ -galactosidase mutant and, for example, an arrestin as a fusion protein with another  $\beta$ -galactosidase mutant. The interaction of arrestin with the GPCR upon receptor activation is measured by enzymatic activity of the complemented  $\beta$ -galactosidase. The test cell is exposed to a test compound, and an increase in  $\beta$ -galactosidase activity indicates the presence of an agonist. The cell is exposed to a test compound and to a GPCR agonist, and reporter enzyme activity is detected. When exposure to the agonist occurs at the same time as or subsequent to exposure to the test compound, a decrease in  $\beta$ -galactosidase activity after exposure to the test compound indicates that the test compound has antagonist activity to the GPCR.

A further aspect of the present invention is a method of screening a sample solution for the presence of an agonist, antagonist or ligand to a G-protein-coupled receptor (GPCR).

A test cell is provided that expresses a GPCR fusion and contains, for example, a  $\beta$ -arrestin protein fusion. The test cell is exposed to a sample solution, and reporter enzyme activity is assessed. Changed reporter enzyme activity after exposure to the sample solution indicates the sample solution contains an agonist, antagonist or ligand for a GPCR expressed in the cell.

5 A further aspect of the present invention is a method of screening a cell for the presence of a G-protein-coupled receptor (GPCR).

A further aspect of the present invention is a method of screening a plurality of cells for those cells which contain a G-protein coupled receptor (GPCR).

A further aspect of the invention is a method for mapping GPCR-mediated signaling  
10 pathways. For instance, the system could be utilized to monitor interaction of c-src with  $\beta$ -arrestin-1 upon GPCR activation. Additionally, the system could be used to monitor protein/protein interactions involved in cross-talk between GPCR signaling pathways and other pathways such as that of the receptor tyrosine kinases or Ras/Raf.

A further aspect of the invention is a method for monitoring homo- or hetero-  
15 dimerization of GPCRs upon agonist or antagonist stimulation.

A further aspect of the invention is a method of screening a cell for the presence of a G-protein-coupled receptor (GPCR) responsive to a GPCR agonist. A cell is provided that contains protein partners that interact downstream in the GPCR's pathway. The protein partners are expressed as fusion proteins to the mutant, complementing enzyme and are used  
20 to monitor activation of the GPCR. The cell is exposed to a GPCR agonist and then enzymatic activity of the reporter enzyme is detected. Increased reporter enzyme activity indicates that the cell contains a GPCR responsive to the agonist.

The invention is achieved by using ICAST™ protein/protein interaction screening to map signaling pathways. This technology is applicable to a variety of known and unknown GPCRs with diverse functions. They include, but are not limited to, the following sub-families of GPCRs:

5 (a) receptors that bind to amine-like ligands-Acetylcholine muscarinic receptor (M1 to M5), alpha and beta Adrenoceptors, Dopamine receptors (D1, D2, D3 and D4), Histamine receptors (H1 and H2), Octopamine receptor and Serotonin receptors (5HT1, 5HT2, 5HT4, 5HT5, 5HT6, 5HT7);

(b) receptors that bind to a peptide ligand-Angiotensin receptor, Bombesin receptor,  
10 Bradykinin receptor, C-C chemokine receptors (CCR1 to CCR8, and CCR10), C-X-C type Chemokine receptors (CXC-R5), Cholecystokinin type A receptor, CCK type receptors, Endothelin receptor, Neurotesin receptor, FMLP-related receptors, Somatostatin receptors (type 1 to type 5) and Opioid receptors (type D, K, M, X);

(c) receptors that bind to hormone proteins- Follic stimulating hormone receptor,  
15 Thyrotrophin receptor and Lutropin-choriogonadotropic hormone receptor;

(d) receptors that bind to neurotransmitters-substance P receptor, Substance K receptor and neuropeptide Y receptor;

(e) Olfactory receptors-Olfactory type 1 to type 11, Gustatory and odorant receptors;

(f) Prostanoid receptors-Prostaglandin E2 (EP1 to EP4 subtypes), Prostacyclin and  
20 Thromboxane;

(g) receptors that bind to metabotropic substances-Metabotropic glutamate group I to group III receptors;

(h) receptors that respond to physical stimuli, such as light, or to chemical stimuli, such as taste and smell; and

(i) orphan GPCRs-the natural ligand to the receptor is undefined.

ICAST™ provides many benefits to the screening process, including the ability to  
5 monitor protein interactions in any sub-cellular compartment-membrane, cytosol and nucleus;  
the ability to achieve a more physiologically relevant model without requiring protein  
overexpression; and the ability to achieve a functional assay for receptor binding allowing  
high information content.

#### BRIEF DESCRIPTION OF THE DRAWINGS

10 FIGURE 1. Cellular expression levels of  $\beta 2$  adrenergic receptor ( $\beta 2AR$ ) and  $\beta$ -  
arrestin-2 ( $\beta Arr2$ ) in C2 clones. Quantification of  $\beta$ -gal fusion protein was performed using  
antibodies against  $\beta$ -gal and purified  $\beta$ -gal protein in a titration curve by a standardized  
ELISA assay. Figure 1A shows expression levels of  $\beta 2AR$ - $\beta gal\Delta\alpha$  clones (in expression  
vector pICAST ALC). Figure 1B shows expression levels of  $\beta Arr2$ - $\beta gal\Delta\omega$  in expression  
15 vector pICAST OMC4 for clones 9-3, -7, -9, -10, -19 and -24, or in expression vector  
pICAST OMN4 for clones 12-4, -9, -16, -18, -22 and -24.

FIGURE 2. Receptor  $\beta 2AR$  activation was measured by agonist-stimulated cAMP  
production. C2 cells expressing pICAST ALC  $\beta 2AR$  (clone 5) or parental cells were treated  
with increasing concentrations of (-)-isoproterenol and 0.1mM IBMX. The quantification of  
20 cAMP level was expressed as pmol/well.

FIGURE 3. Interaction of activated receptor  $\beta$ 2AR and arrestin can be measured by  $\beta$ -galactosidase complementation. Figure 3A shows a time course of  $\beta$ -galactosidase activity in response to agonist (-)isoproterenol stimulation in C2 expressing  $\beta$ 2AR- $\beta$ gal $\Delta\alpha$  ( $\beta$ 2AR alone, in expression vector pICAST ALC), or C2 clones, and a pool of C2 co-expressing  $\beta$ 2AR- $\beta$ gal $\Delta\alpha$  and  $\beta$ Arr2- $\beta$ gal $\Delta\omega$  (in expression vectors pICAST ALC and pICAST OMC). Figure 3B shows a time course of  $\beta$  galactosidase activity in response to agonist (-)isoproterenol stimulation in C2 cells expressing  $\beta$ 2AR alone (in expression vector pICAST ALC) and C2 clones co-expressing  $\beta$ 2AR and  $\beta$ Arr1 (in expression vectors ICAST ALC and pICAST OMC).

FIGURE 4. Agonist dose response for interaction of  $\beta$ 2AR and arrestin can be measured by  $\beta$ -galactosidase complementation. Figure 4A shows a dose response to agonists (-)isoproterenol and procaterol in C2 cells co-expressing pICAST ALC  $\beta$ 2AR and pICAST OMC  $\beta$ Arr2 fusion constructs. Figure 4B shows a dose response to agonists (-)isoproterenol and procaterol in C2 cells co-expressing pICAST ALC  $\beta$ 2AR and pICAST OMC  $\beta$ Arr1 fusion constructs.

FIGURE 5. Antagonist mediated inhibition of receptor activity can be measured by  $\beta$ -galactosidase complementation in cells co-expressing  $\beta$ 2AR- $\beta$ gal $\Delta\alpha$  and  $\beta$ Arr- $\beta$ gal $\Delta\omega$ . Figure 5A shows specific inhibition with adrenergic antagonists ICI-118,551 and propranolol of  $\beta$ -galactosidase activity in C2 clones co-expressing pICAST ALC  $\beta$ 2AR and pICAST OMC  $\beta$ Arr2 fusion constructs after incubation with agonist (-)isoproterenol. Figure 5B shows specific inhibition of  $\beta$ -galactosidase activity with adrenergic antagonists ICI-118,551

and propranolol in C2 clones co-expressing pICAST ALC  $\beta$ 2AR and pICAST OMC  $\beta$ Arr1 fusion constructs in the presence of agonist (-)isoproterenol.

FIGURE 6. C2 cells expressing adenosine receptor A2a show cAMP induction in response to agonist (CGC-21680) treatment. C2 parental cells and C2 cells co-expressing pICAST ALC A2aR and pICAST OMC  $\beta$ Arr1 as a pool or as selected clones were measured for agonist-induced cAMP response (pmol/well).

FIGURE 7. Agonist stimulated cAMP response in C2 cells co-expressing Dopamine receptor D1 (D1- $\beta$ gal $\Delta\alpha$ ) and  $\beta$ -arrestin-2 ( $\beta$ Arr2- $\beta$ gal $\Delta\omega$ ). The clone expressing  $\beta$ Arr2- $\beta$ gal $\Delta\omega$  (Arr2 alone) was used as a negative control in the assay. Cells expressing D1- $\beta$ gal $\Delta\alpha$  in addition to  $\beta$ Arr2- $\beta$ gal $\Delta\omega$  responded agonist treatment (3-hydroxytyramine hydrochloride at 3  $\mu$ M). D1(PIC2) or D1(PIC3) designate D1 in expression vector pICAST ALC2 or pICAST ALC4, respectively.

FIGURE 8. Variety of mammalian cell lines can be used to generate stable cells for monitoring GPCR and arrestin interactions. FIGURE 8A, FIGURE 8B and FIGURE 8C show the examples of HEK293, CHO and CHW cell lines co-expressing adrenergic receptor  $\beta$ 2AR and arrestin fusion proteins of  $\beta$ -galactosidase mutants. The  $\beta$ -galactosidase activity was used to monitor agonist-induced interaction of  $\beta$ 2AR and arrestin proteins.

FIGURE 9. Beta-gal complementation can be used to monitor  $\beta$ 2 adrenergic receptor homo-dimerization. FIGURE 9A shows  $\beta$ -galactosidase activity in HEK293 clones co-expressing pICAST ALC  $\beta$ 2AR and pICAST OMC  $\beta$ 2AR. FIGURE 9B shows a cAMP response to agonist (-)isoproterenol in HEK 293 clones co-expressing pICAST ALC  $\beta$ 2AR



and pICAST OMC  $\beta$ 2AR. HEK293 parental cells were included in the assays as negative controls.

FIGURE 10A. pICAST ALC: Vector for expression of  $\beta$ -gal $\Delta\alpha$  as a C-terminal fusion to the target protein. This construct contains the following features: MCS, multiple cloning site for cloning the target protein in frame with the  $\beta$ -gal $\Delta\alpha$ ; GS Linker, (GGGGS)<sub>n</sub>; NeoR, neomycin resistance gene; IRES, internal ribosome entry site; ColE1ori, origin of replication for growth in *E. coli*; 5'MoMuLV LTR and 3'MoMuLV LTR, viral promotor and polyadenylation signals from the Moloney Murine leukemia virus.

FIGURE 10B. Nucleotide sequence for pICAST ALC.

FIGURE 11A. pICAST ALN: Vector for expression of  $\beta$ -gal $\Delta\alpha$  as an N-terminal fusion to the target protein. This construct contains the following features: MCS, multiple cloning site for cloning the target protein in frame with the  $\beta$ -gal $\Delta\alpha$ ; GS Linker, (GGGGS)<sub>n</sub>; NeoR, neomycin resistance gene; IRES, internal ribosome entry site; ColE1ori, origin of replication for growth in *E. coli*; 5'MoMuLV LTR and 3'MoMuLV LTR, viral promotor and polyadenylation signals from the Moloney Murine leukemia virus.

FIGURE 11B. Nucleotide sequence for pICAST ALN.

FIGURE 12A. pICAST OMC: Vector for expression of  $\beta$ -gal $\Delta\omega$  as a C-terminal fusion to the target protein. This construct contains the following features: MCS, multiple cloning site for cloning the target protein in frame with the  $\beta$ -gal $\Delta\omega$ ; GS Linker, (GGGGS)<sub>n</sub>; Hygro, hygromycin resistance gene; IRES, internal ribosome entry site; ColE1ori, origin of replication for growth in *E. coli*; 5'MoMuLV LTR and 3'MoMuLV LTR, viral promotor and polyadenylation signals from the Moloney Murine leukemia virus.

FIGURE 12B. Nucleotide sequence for pICAST OMC.

FIGURE 13A. pICAST OMN: Vector for expression of  $\beta$ -gal $\Delta\omega$  as an N-terminal fusion to the target protein. This construct contains the following features: MCS, multiple cloning site for cloning the target protein in frame with the  $\beta$ -gal $\Delta\omega$ ; GS Linker, (GGGGS)<sub>n</sub>; Hygro, hygromycin resistance gene; IRES, internal ribosome entry site; ColE1 ori, origin of replication for growth in E. coli; 5'MoMuLV LTR and 3'MoMuLV LTR, viral promotor and polyadenylation signals from the Moloney Murine leukemia virus.

FIGURE 13B. Nucleotide sequence for pICAST OMN.

FIGURE 14. pICAST ALC  $\beta$ Arr2: Vector for expression of  $\beta$ -gal $\Delta\alpha$  as a C-terminal fusion to  $\beta$ -arrestin-2. The coding sequence of human  $\beta$ -arrestin-2 (Genebank Accession Number: NM\_004313) was cloned in frame to  $\beta$ -gal $\Delta\alpha$  in a pICAST ALC vector.

FIGURE 15. pICAST OMC  $\beta$ Arr2: Vector for expression of  $\beta$ -gal $\Delta\omega$  as a C-terminal fusion to  $\beta$ -arrestin-2. The coding sequence of human  $\beta$ -arrestin-2 (Genebank Accession Number: NM\_004313) was cloned in frame to  $\beta$ -gal $\Delta\omega$  in a pICAST OMC vector.

FIGURE 16. pICAST ALC  $\beta$ Arr1: Vector for expression of  $\beta$ -gal $\Delta\alpha$  as a C-terminal fusion to  $\beta$ -arrestin-1. The coding sequence of human  $\beta$ -arrestin-1 (Genebank Accession Number: NM\_004041) was cloned in frame to  $\beta$ -gal $\Delta\alpha$  in a pICAST ALC vector.

FIGURE 17. pICAST OMC  $\beta$ Arr1: Vector for expression of  $\beta$ -gal $\Delta\omega$  as a C-terminal fusion to  $\beta$ -arrestin-1. The coding sequence of human  $\beta$ -arrestin-1 (Genebank Accession Number: NM\_004041) was cloned in frame to  $\beta$ -gal $\Delta\omega$  in a pICAST OMC vector.

FIGURE 18. pICAST ALC  $\beta$ 2AR: Vector for expression of  $\beta$ -gal $\Delta\alpha$  as a C-terminal fusion to  $\beta$ 2 Adrenergic Receptor. The coding sequence of human  $\beta$ 2 Adrenergic Receptor

(Genebank Accession Number: NM\_000024) was cloned in frame to  $\beta$ -gal $\Delta\alpha$  in a pICAST ALC vector.

FIGURE 19. pICAST OMC  $\beta$ 2AR: Vector for expression of  $\beta$ -gal $\Delta\omega$  as a C-terminal fusion  $\beta$ 2 Adrenergic Receptor. The coding sequence of human  $\beta$ 2 Adrenergic Receptor (Genebank Accession Number: NM\_000024) was cloned in frame to  $\beta$ -gal $\Delta\omega$  in a pICAST OMC vector.

FIGURE 20. pICAST ALC A2aR: Vector for expression of  $\beta$ -gal $\Delta\alpha$  as a C-terminal fusion to Adenosine 2a Receptor. The coding sequence of human Adenosine 2a Receptor (Genebank Accession Number: NM\_000675) was cloned in frame to  $\beta$ -gal $\Delta\alpha$  in a pICAST ALC vector.

FIGURE 21. pICAST OMC A2aR: Vector for expression of  $\beta$ -gal $\Delta\omega$  as a C-terminal fusion to Adenosine 2a Receptor. The coding sequence of human Adenosine 2a Receptor (Genebank Accession Number: NM\_000675) was cloned in frame to  $\beta$ -gal $\Delta\omega$  in a pICAST OMC vector.

FIGURE 22. pICAST ALC D1: Vector for expression of  $\beta$ -gal $\Delta\alpha$  as a C-terminal fusion to Dopamine D1 Receptor. The coding sequence of human Dopamine D1 Receptor (Genebank Accession Number: X58987) was cloned in frame to  $\beta$ -gal $\Delta\alpha$  in a pICAST ALC vector.

FIGURE 23. A schematic depicting the method of the invention, which shows that two inactive mutants that become active when they interact.

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

All literature and patents cited in this disclosure are incorporated herein by reference.

The present invention provides a method to interrogate GPCR function and pathways.

The G-protein-coupled superfamily continues to expand rapidly as new receptors are  
5 discovered through automated sequencing of cDNA libraries or genomic DNA. It is  
estimated that several thousand GPCRs may exist in the human genome, as many as 250  
GPCRs have been cloned and only as few as 150 have been associated with ligands. The  
means by which these, or newly discovered orphan receptors, will be associated with their  
cognate ligands and physiological functions represents a major challenge to biological and  
10 biomedical research. The identification of an orphan receptor generally requires an  
individualized assay and a guess as to its function. The interrogation of a GPCR's signaling  
behavior by introducing a replacement receptor eliminates these prerequisites because it can  
be performed with and without prior knowledge of other signaling events. It is sensitive,  
rapid and easily performed and should be applicable to nearly all GPCRs because the  
15 majority of these receptors should desensitize by a common mechanism.

Various approaches have been used to monitor intracellular activity in response to a  
stimulant, e.g., enzyme-linked immunosorbent assay (ELISA); Fluorescence Imaging Plate  
Reader assay (FLIPR™, Molecular Devices Corp., Sunnyvale, CA); EVOscreen™,  
EVOTEC™, Evotec Biosystems GmbH, Hamburg, Germany; and techniques developed by  
20 CELLOMICS™, Cellomics, Inc., Pittsburgh, PA.

Germino, F.J., et al., "Screening for in vivo protein-protein interactions." Proc. Natl.  
Acad. Sci., 90(3): 933-7 (1993), discloses an *in vivo* approach for the isolation of proteins  
interacting with a protein of interest.

Phizicky, E.M., et al., "Protein-protein interactions: methods for detection and analysis." Microbiol. Rev., 59(1): 94-123 (1995), discloses a review of biochemical, molecular biological and genetic methods used to study protein-protein interactions.

Offermanns, et al., " $G\alpha_{15}$  and  $G\alpha_{16}$  Couple a Wide Variety of Receptors to Phospholipase C." J. Biol. Chem., 270(25):15175-80 (1995), discloses that  $G\alpha_{15}$  and  $G\alpha_{16}$  can be activated by a wide variety of G-protein-coupled receptors. The selective coupling of an activated receptor to a distinct pattern of G-proteins is regarded as an important requirement to achieve accurate signal transduction. Id.

Barak et al., "A  $\beta$ -arrestin/Green Fluorescent Protein Biosensor for Detecting G Protein-coupled Receptor Activation." J. Biol. Chem., 272(44):27497-500 (1997) and U.S. Patent No. 5,891,646, disclose the use of a  $\beta$ -arrestin/green fluorescent fusion protein (GFP) to monitor protein translocation upon stimulation of GPCR.

The present invention involves a method for monitoring protein-protein interactions in GPCR pathways as a complete assay using ICAST™ (Intercistronic Complementation Analysis Screening Technology as disclosed in pending U.S. patent application serial no. 053,164, filed April 1, 1998, the entire contents of which are incorporated herein by reference). This invention enables an array of assays, including GPCR binding assays, to be achieved directly within the cellular environment in a rapid, non-radioactive assay format amenable to high-throughput screening. Using existing technology, assays of this type are currently performed in a non-cellular environment and require the use of radioisotopes.

The present invention combined with Tropix ICAST™ and Advanced Discovery Sciences™ technologies, e.g., ultra high-throughput screening, provide highly sensitive cell-based methods for interrogating GPCR pathways which are amendable to high-throughput

screening (HTS). These methods are an advancement over the invention disclosed in U.S. Patent 5,891,646, which relies on microscopic imaging of GPCR components as fusion with Green-fluorescent-protein. Imaging techniques are limited by low-throughput, lack of thorough quantification and low signal to noise ratios. Unlike yeast-based-2-hybrid assays  
5 used to monitor protein/protein interactions in high-throughput assays, the present invention is applicable to a variety of cells including mammalian cells, plant cells, protozoa cells such as *E. coli* and cells of invertebrate origin such as yeast, slime mold (*Dictyostelium*) and insects; detects interactions at the site of the receptor target or downstream target proteins rather than in the nucleus; and does not rely on indirect read-outs such as transcriptional  
10 activation. The present invention provides assays with greater physiological relevance and fewer false negatives.

Advanced Discovery Sciences™ is in the business of offering custom-developed screening assays optimized for individual assay requirements and validated for automation. These assays are designed by HTS experts to deliver superior assay performance. Advanced  
15 Discovery Sciences™ custom assay development service encompasses the design, development, optimization and transfer of high performance screening assays. Advanced Discovery Sciences™ works to design new assays or convert existing assays to ultra-sensitive luminescent assays ready for the rigors of HTS. Among some of the technologies developed by Advanced Discovery Sciences™ are the cAMP-Screen™ immunoassay system. This  
20 system provides ultrasensitive determination of cAMP levels in cell lysates. The cAMP-Screen™ assay utilizes the high-sensitivity chemiluminescent alkaline phosphatase (AP) substrate CSPD® with Sapphire-II™ luminescence enhancer.

**EXAMPLE:**

GPCR activation can be measured through monitoring the binding of ligand-activated GPCR by an arrestin. In this assay system, a GPCR, e.g.  $\beta$  adrenergic receptor ( $\beta$  2AR) and a  $\beta$  arrestin are co-expressed in the same cell as fusion proteins with  $\beta$  gal mutants. As illustrated in Figure 1, the  $\beta$ 2AR is expressed as a fusion protein with  $\Delta\alpha$  form of  $\beta$  gal mutant ( $\beta$ 2ADR $\Delta\alpha$ ) and the  $\beta$  arrestin as a fusion protein with the  $\Delta\omega$  mutant of  $\beta$  gal ( $\beta$ -Arr $\Delta\omega$ ). The two fusion proteins exist inside of a resting (or un-stimulated) cell in separate compartments, i.e. membrane for GPCR and cytosol for arrestin, and they can not form an active  $\beta$  galactosidase enzyme. When such a cell is treated with an agonist or a ligand, the ligand-occupied and activated receptor will become a high affinity binding site for Arrestin. The interaction between an activated  $\beta$ 2ADR $\Delta\alpha$  and  $\beta$ -Arr $\Delta\omega$  drives the  $\beta$  gal gal mutant complementation. The enzyme activity can be measured by using an enzyme substrate, which upon cleavage releases a product measurable by colorimetry, fluorescence, chemiluminescence (e.g. Tropix product GalScreen<sup>TM</sup>).

**Experiment protocol-**

1. In the first step, the expression vectors for  $\beta$ 2ADR $\Delta\alpha$  and  $\beta$ Arr2 $\Delta\omega$  were engineered in selectable retroviral vectors pICAST ALC, as described in Figure 18 and pICAST OMC, as in Figure 15.
2. In the second step, the two expression constructs were transduced into either C2C12 myoblast cells, or other mammalian cell lines, such as COS-7, CHO, A431, HEK 293, and CHW. Following selection with antibiotic drugs, stable clones expressing both fusion

proteins at appropriate levels were selected.

3. In the last step, the cells expressing both  $\beta 2\text{ADR}\Delta\alpha$  and  $\beta\text{Arr}2\Delta\omega$  were tested for response by agonist/ligand stimulated  $\beta$  galactosidase activity. Triplicate samples of cells were plated at 10,000 cells in 100 microliter volume into a well of 96-well culture plate. Cells were cultured for 24 hours before assay. For agonist assay (Figure 3 and 4), cells were treated with variable concentrations of agonist, for example, (-) isoproterenol, procaterol, dobutamine, terbutiline or L-L-phenylephrine for 60 min at 37 C. The induced  $\beta$  galactosidase activity was measured by addition of Tropix GalScreen<sup>TM</sup> substrate (Applied Biosystems) and luminescence measured in a Tropix TR717<sup>TM</sup> luminometer (Applied Biosystems). For antagonist assay (Figure 5), cells were pre-incubated for 10 min in fresh medium without serum in the presence of ICI-118,551 or propranolol followed by addition of 10 micro molar (-) isoproterenol.

The assays of this invention, and their application and preparation have been described both generically, and by specific example. The examples are not intended as limiting. Other substituent identities, characteristics and assays will occur to those of ordinary skill in the art, without the exercise of inventive faculty. Such modifications remain within the scope of the invention, unless excluded by the express recitation of the claims advanced below.



**WHAT IS CLAIMED IS:**

1. A method of assessing the effect of a test condition on G-protein-coupled receptor (GPCR) pathway activity, comprising:

- 5 a) providing a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an interacting protein partner as a fusion to another mutant form of enzyme;
- b) exposing the cell to a ligand for said GPCR under said test condition; and
- c) monitoring activation of said GPCR by complementation of said reporter enzyme;
- 10 wherein increased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates increased GPCR interaction with its interacting protein partner compared to that which occurs in the absence of said test condition, and decreased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates decreased GPCR interaction with its interacting protein partner compared to that which occurs in the absence of said test condition.

15 2. A method according to Claim 1, wherein the test condition is the presence in the cell of a kinase.

3. A method according to Claim 1, wherein the test condition is the presence in the cell of a G-protein.

20 4. A method according to Claim 1, wherein the test condition is the exposure of the cell to a compound selected from GPCR agonists and GPCR antagonists.

5. A method according to Claim 1, wherein the test condition is co-expression in the cell of a second receptor.

6. A method according to Claim 5, wherein the second receptor is a GPCR receptor.

7. A method according to Claim 5, wherein homo-dimerization of GPCR is determined.

8. A method according to Claim 5, wherein hetero-dimerization of GPCR is determined.

5        9. A method for screening a  $\beta$ -arrestin protein or an unidentified arrestin or arrestin-like protein or fragment and mutant form thereof for the ability to bind to activated GPCRs, comprising:

a) providing a cell that:

i) expresses at least one GPCR as a fusion protein to a reporter enzyme; and

10        ii) contains a conjugate comprising a test  $\beta$ -arrestin protein as a fusion protein with another reporter enzyme;

b) exposing the cell to a ligand for said at least one GPCR; and

c) detecting enzymatic activity of the complemented reporter enzyme;

wherein an increase in enzymatic activity in the cell indicates  $\beta$ -arrestin protein

15        binding to the activated GPCR.

10. A method for screening a test compound for G-protein-coupled receptor (GPCR) agonist activity, comprising:

a) providing a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin protein as a fusion to another mutant form of enzyme;

20        b) exposing the cell to a test compound; and

c) detecting complementation of said reporter enzyme;

wherein increased reporter enzyme activity after exposure of the cell to the test compound indicates GPCR agonist activity of the test compound.

11. A method according to Claim 10, wherein the cell expresses a GPCR whose function is known.

12. A method according to Claim 10, wherein the cell expresses a GPCR whose function is unknown.

5 13. A method according to Claim 10, wherein the cell expresses an odorant or taste GPCR.

14. A method according to Claim 10, wherein the cell expresses a GPCR a  $\beta$ -adrenergic GPCR.

10 15. A method according to Claim 10, wherein the cell is selected from the group consisting of mammalian cells, cells of invertebrate origin, plant cells and protozoa cells.

16. A method according to Claim 10, wherein the cell endogenously expresses a GPCR.

17. A method according to Claim 10, wherein the cell has been transformed to express a GPCR not endogenously expressed by such a cell.

15 18. A method of screening a test compound for G-protein-coupled receptor (GPCR) antagonist activity, comprising:

a) providing a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin protein as a fusion to another mutant form of enzyme;

b) exposing the cell to said test compound;

20 c) exposing the cell to an agonist for said GPCR; and

d) detecting complementation of said reporter enzyme;

where exposure to the agonist occurs at the same time as, or subsequent to, exposure to the test compound, and wherein decreased reporter enzyme activity after exposure of the

cell to the test compound indicates that the test compound is an antagonist for said GPCR.

19. A method of screening a cell for the presence of a G-protein-coupled receptor (GPCR) responsive to a GPCR agonist, comprising:

- a) providing a cell, said cell containing a conjugate comprising a  $\beta$ -arrestin protein as  
5 a fusion protein with a reporter enzyme;
- b) exposing the cell to a GPCR agonist; and
- c) detecting enzymatic activity of the reporter enzyme;

wherein an increase in enzymatic activity after exposure of the cell to the GPCR agonist indicates that the cell contains a GPCR responsive to said agonist.

10 20. A method of screening a plurality of cells for those cells which contain a G-protein-coupled receptor (GPCR) responsive to a GPCR agonist, comprising:

- a) providing a plurality of cells, said cells containing a conjugate comprising a  
15  $\beta$ -arrestin protein as a fusion protein with a reporter enzyme;
- b) exposing the cells to a GPCR agonist; and
- c) detecting enzymatic activity of the reporter enzyme;

wherein an increase in enzymatic activity after exposure to the GPCR agonist indicates  $\beta$ -arrestin protein binding to a GPCR, thereby indicating that the cell contains a GPCR responsive to said GPCR agonist.

20 21. A method according to Claim 20, wherein the plurality of cells are contained in a tissue.

22. A method according to Claim 20, wherein the plurality of cells are contained in an organ.

23. A method according to Claim 20, wherein step (b) comprises exposing the cells to a plurality of GPCR agonists or ligand libraries.

24. A substrate having deposited thereon a plurality of cells, said cells expressing at least one GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin protein as a fusion to another mutant form of enzyme.

25. A substrate according to Claim 24, wherein the substrate contains an enzyme-labile chemical group which, upon cleavage by the reporter enzyme, releases a product measurable by colorimetry, fluorescence or chemiluminescence.

26. A substrate according to Claim 24, wherein the substrate is made of a material selected from glass, plastic, ceramic, semiconductor, silica, fiber optic, diamond, biocompatible monomer and biocompatible polymer materials.

27. A method of detecting G-protein-coupled receptor (GPCR) pathway activity in a cell expressing at least one GPCR and containing  $\beta$ -arrestin protein as a fusion protein with a reporter enzyme; wherein said enzymatic activity indicates activation of the GPCR pathway.

28. A method according to Claim 27, where the cells are deposited on a substrate prior to detecting said enzymatic activity.

29. A method according to Claim 27, wherein said cell is contained in a tissue.

30. A method according to Claim 27, wherein said cell is contained in an organ.

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Cellular Expression of  $\beta_2$ AR- $\beta$ gal  $\Delta\alpha$  Fusion Protein in C2 Clones  
(measured by anti- $\beta$ -gal ELISA)

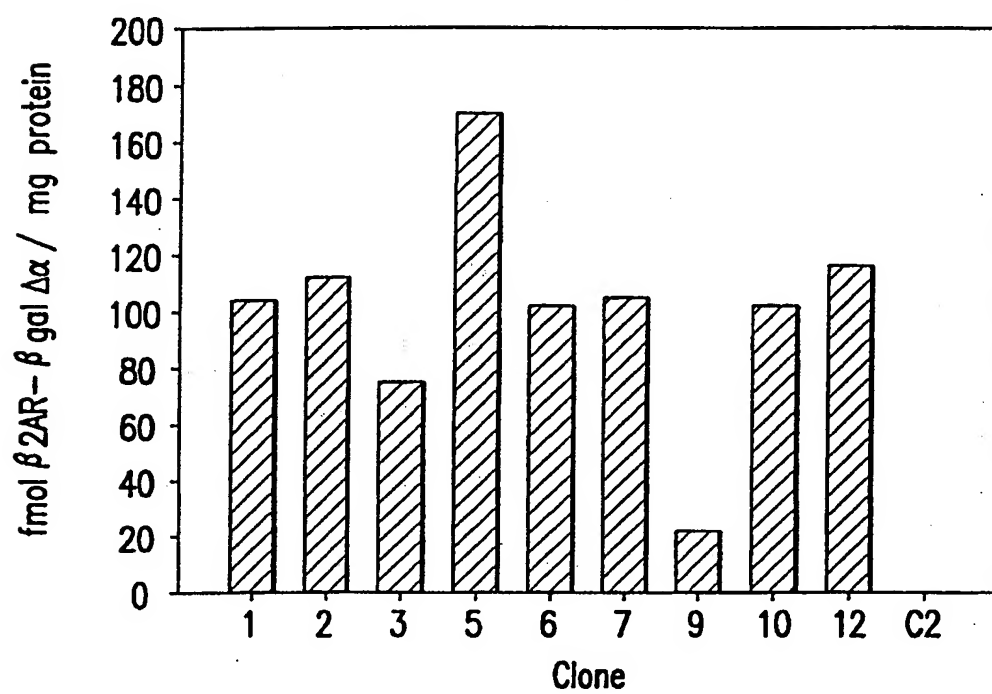


FIG. 1A

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Cellular expression of  $\beta$ Arr- $\beta$ gal  $\Delta\omega$  fusion protein in C2 clones  
(measured by anti- $\beta$  gal ELISA)

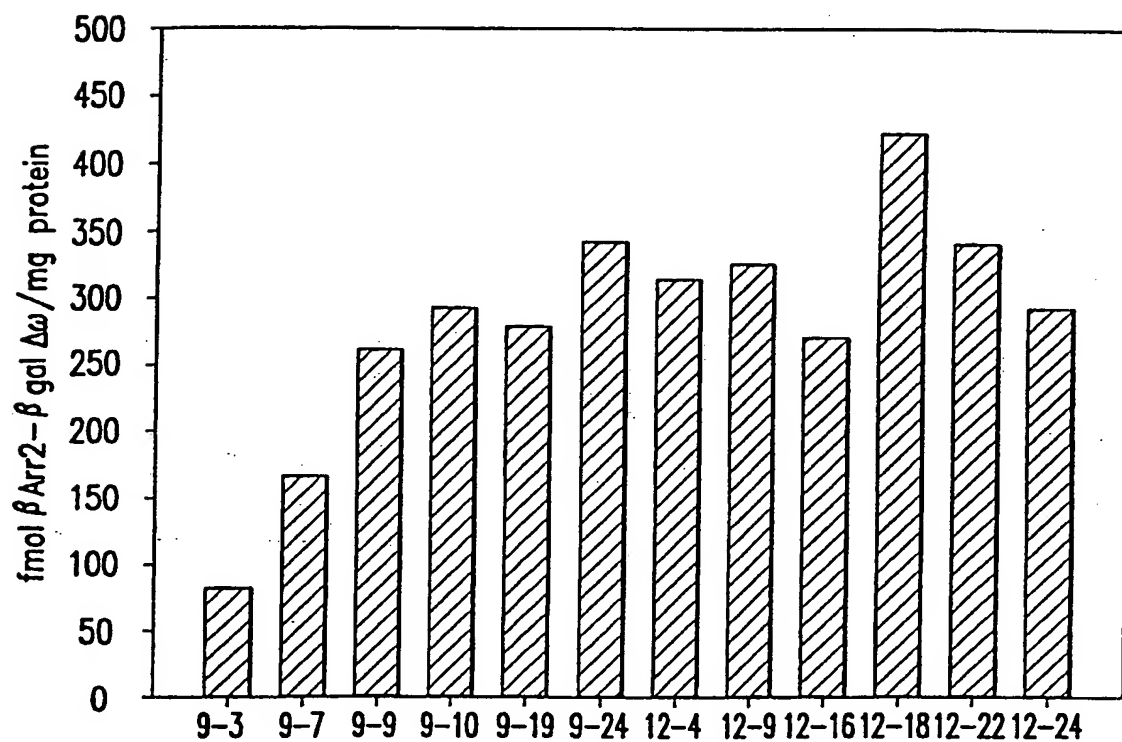


FIG. 1B

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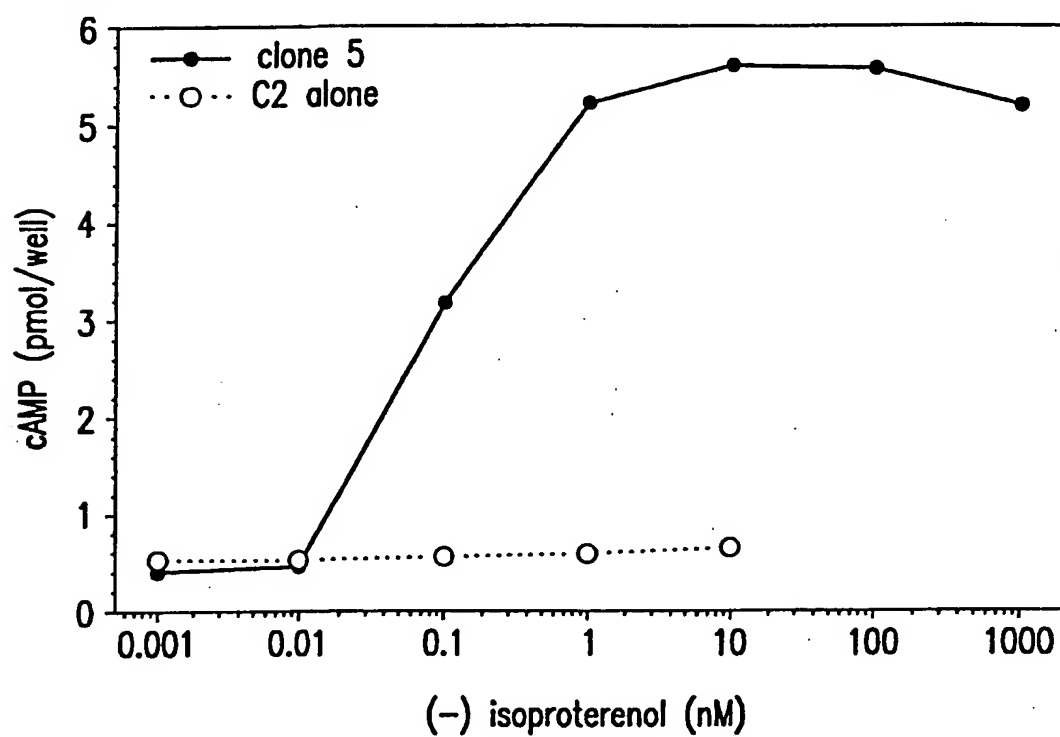
Agonist Stimulated cAMP Response in C2 Cells Expressing  $\beta 2AR-\beta gal\Delta\alpha$ 

FIG.2



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$\beta$ -galactosidase Complementation as a Measurement for  $\beta_2$ AR- $\beta$ gal $\Delta\alpha$  interacting with  $\beta$ Arrestin2- $\beta$ gal $\Delta\omega$  upon agonist Stimulation

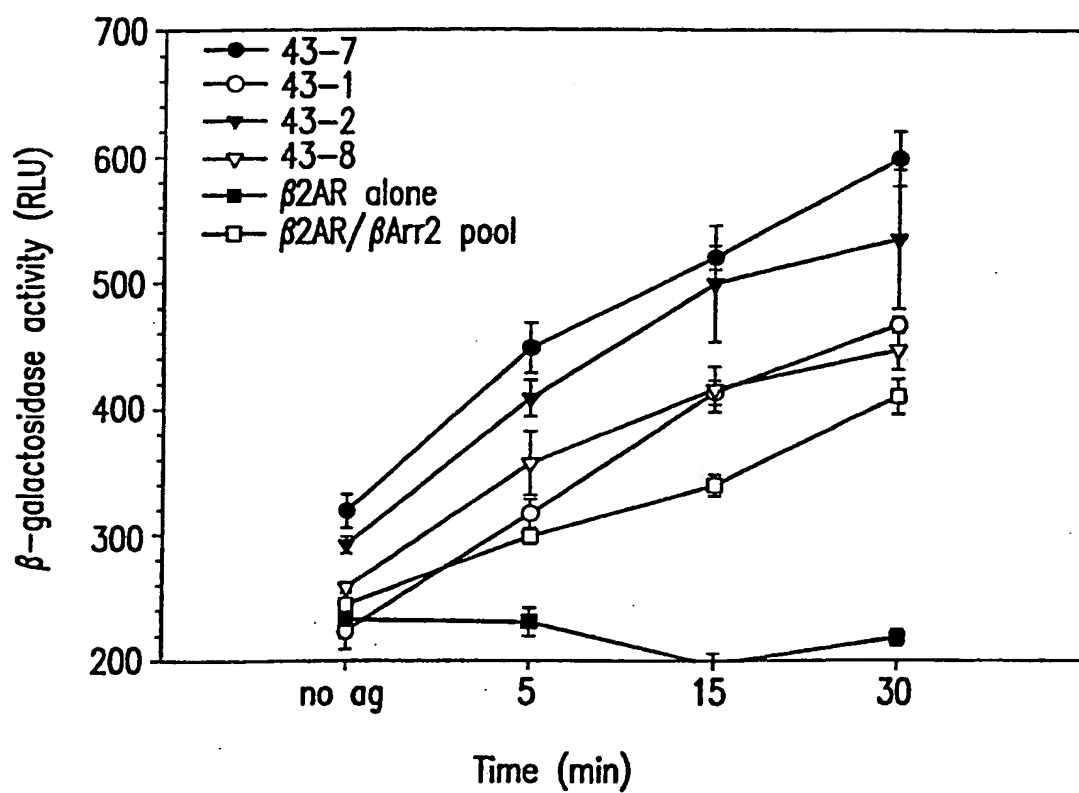


FIG. 3A

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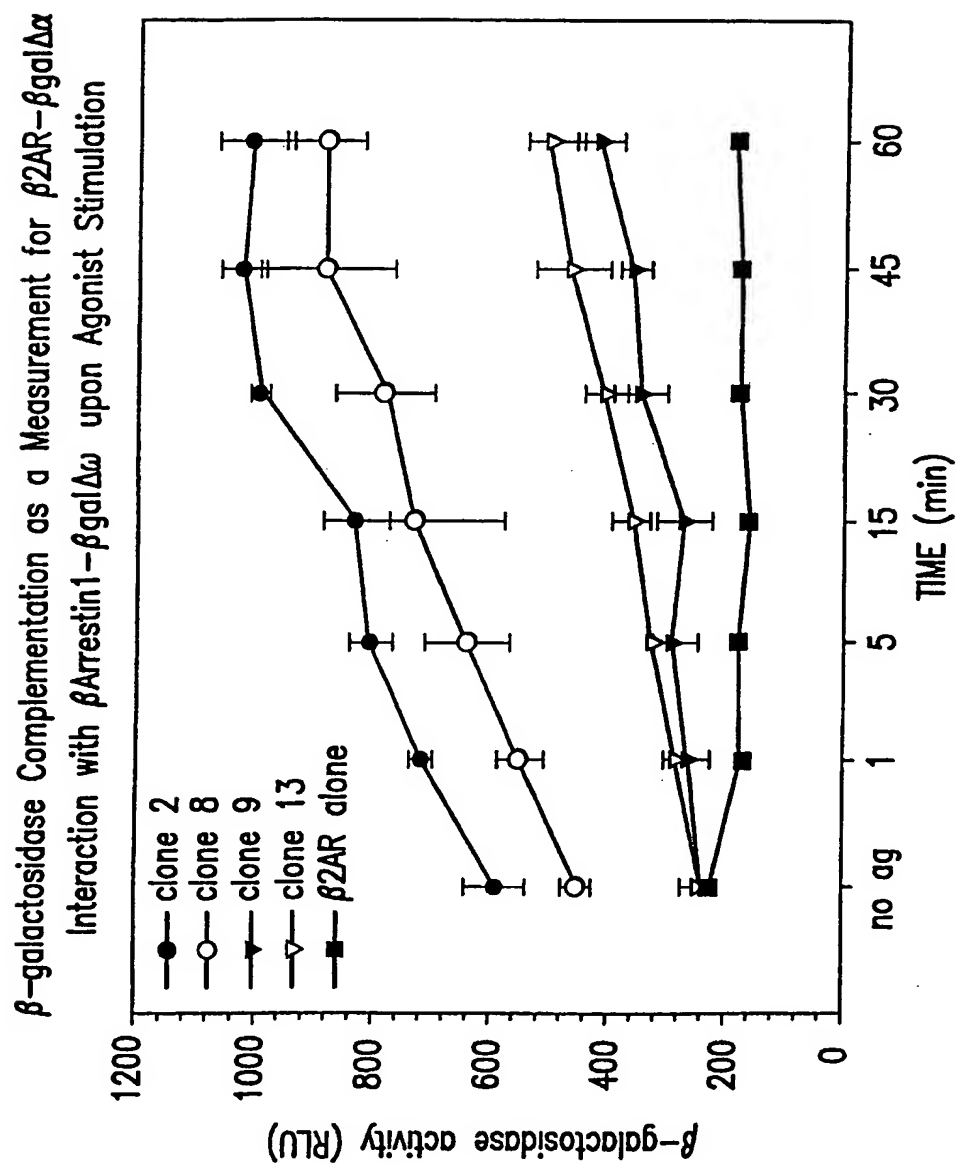


FIG. 3B

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$\beta$ -galactosidase Activity in Response to Agonist in C2 Cells  
Coexpressing  $\beta$ 2AR- $\beta$ gal $\Delta\alpha$  and  $\beta$ Arrestin2- $\beta$ gal $\Delta\omega$  Fusion Proteins

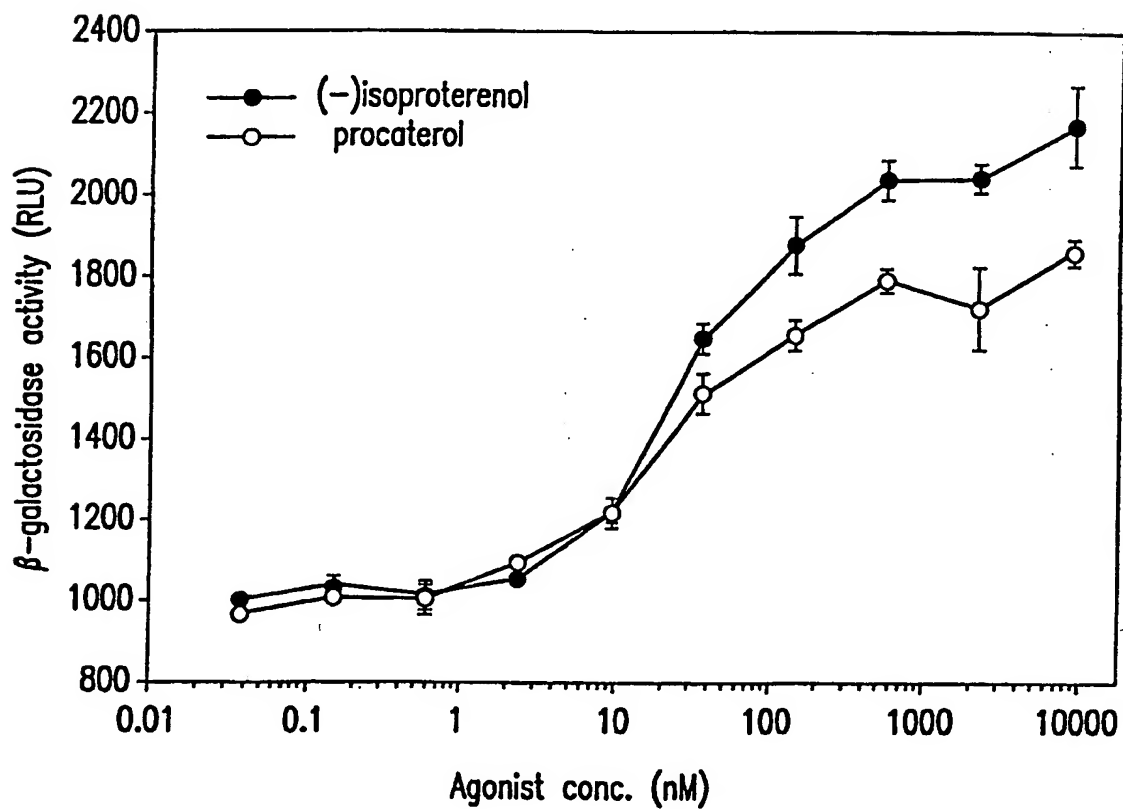


FIG. 4A

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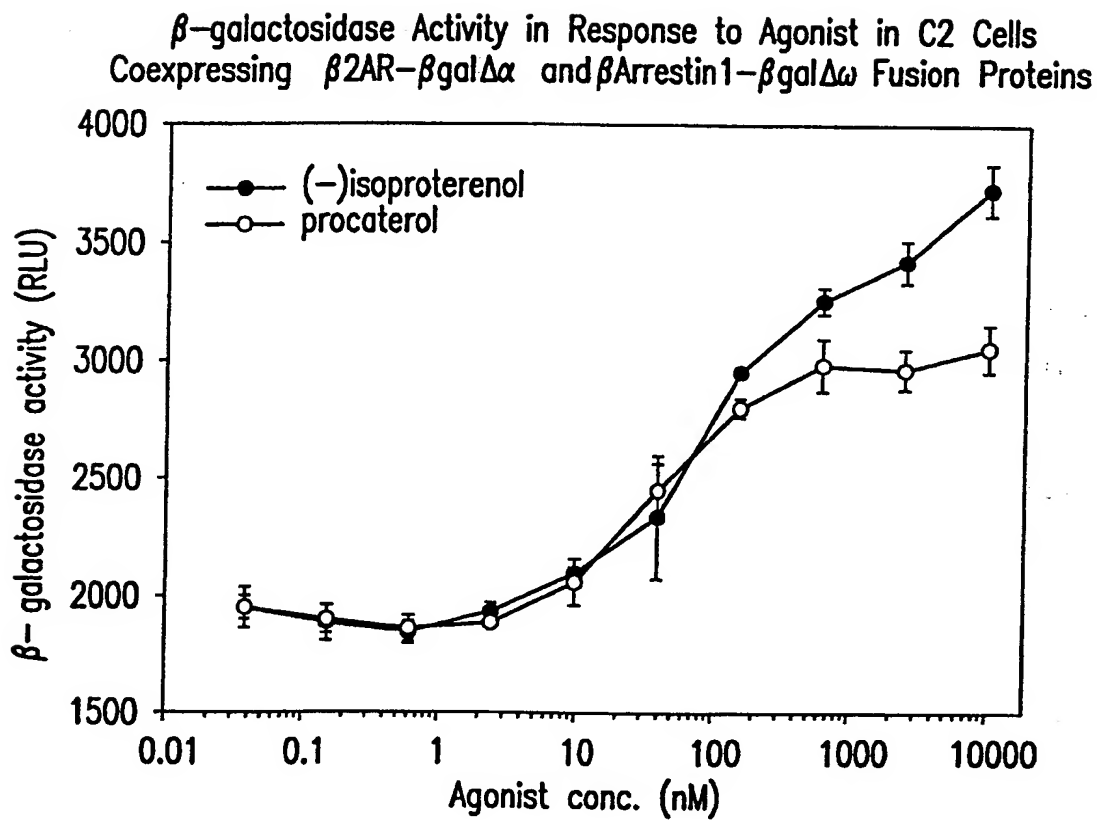


FIG. 4B

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Inhibition of  $\beta$ -galactosidase activity in C2 Cells Coexpressing  $\beta$ 2AR- $\beta$ gal $\Delta\alpha$  and  $\beta$ Arrestin2- $\beta$ gal $\Delta\omega$  Fusion Proteins

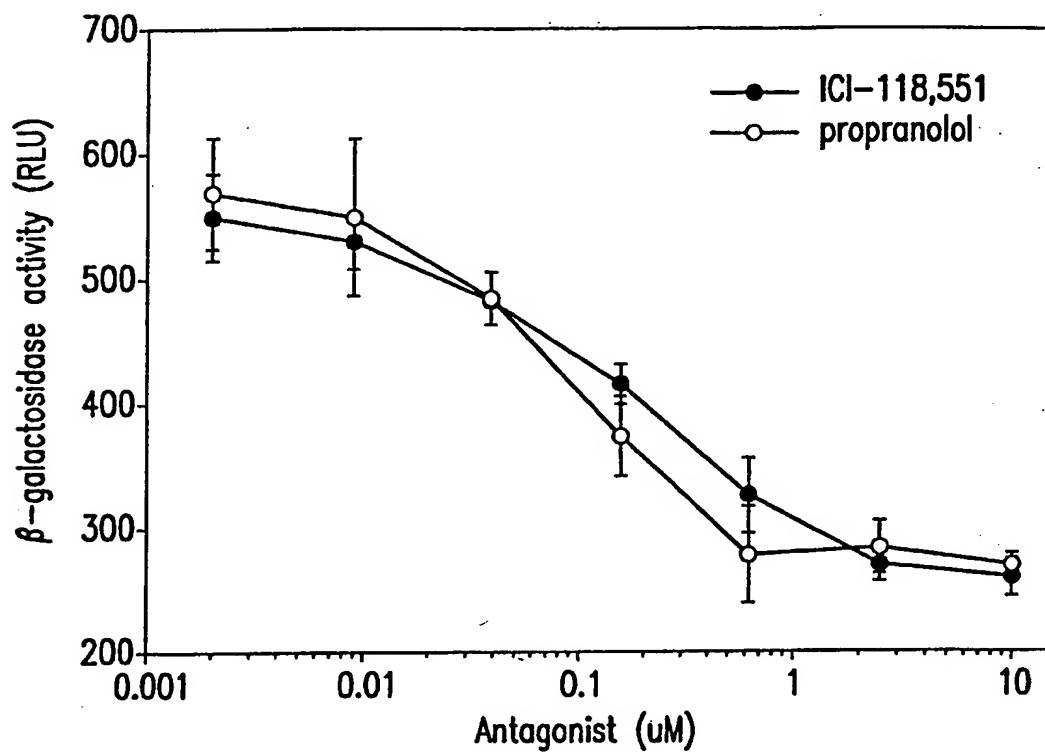


FIG. 5A

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Antagonist Inhibition of  $\beta$ -galactosidase Activity in C2 Cells  
Coexpressing  $\beta$ 2AR- $\beta$ gal $\Delta\alpha$  and  $\beta$ Arrestin1- $\beta$ gal $\Delta\omega$  Fusion Proteins

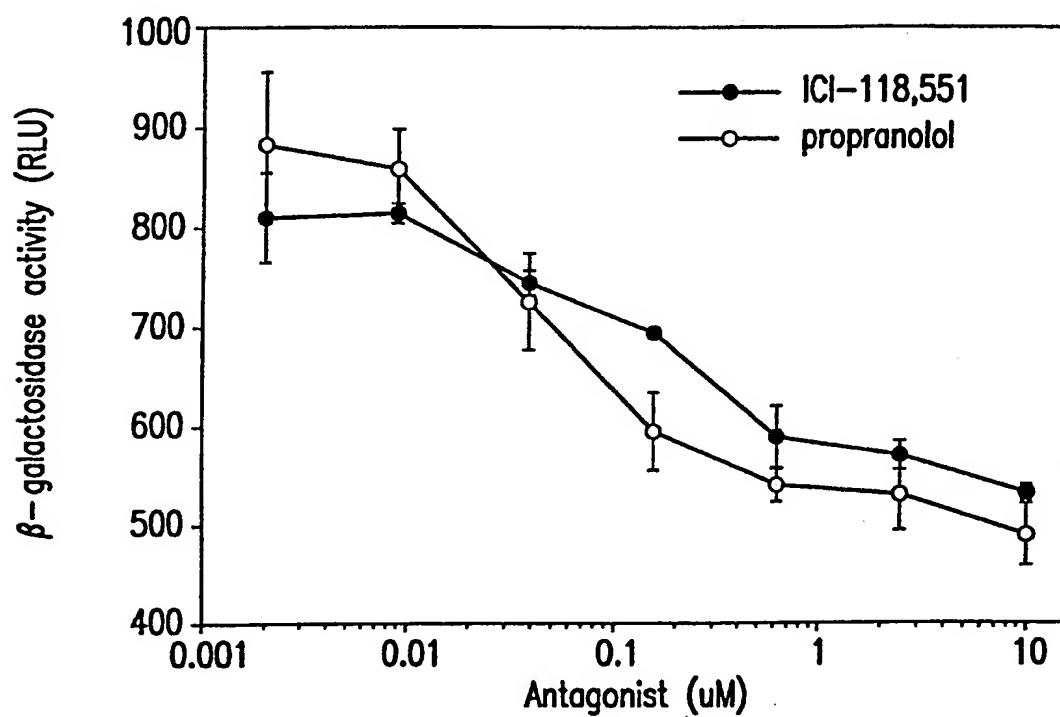


FIG. 5B

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Agonist Stimulated cAMP Response in Clones or Pools of C2 Cells  
Coexpressing A2aR- $\beta$ gal  $\Delta\alpha$  and  
 $\beta$ Arrestin1-  $\beta$ gal  $\Delta\omega$  Fusion Proteins

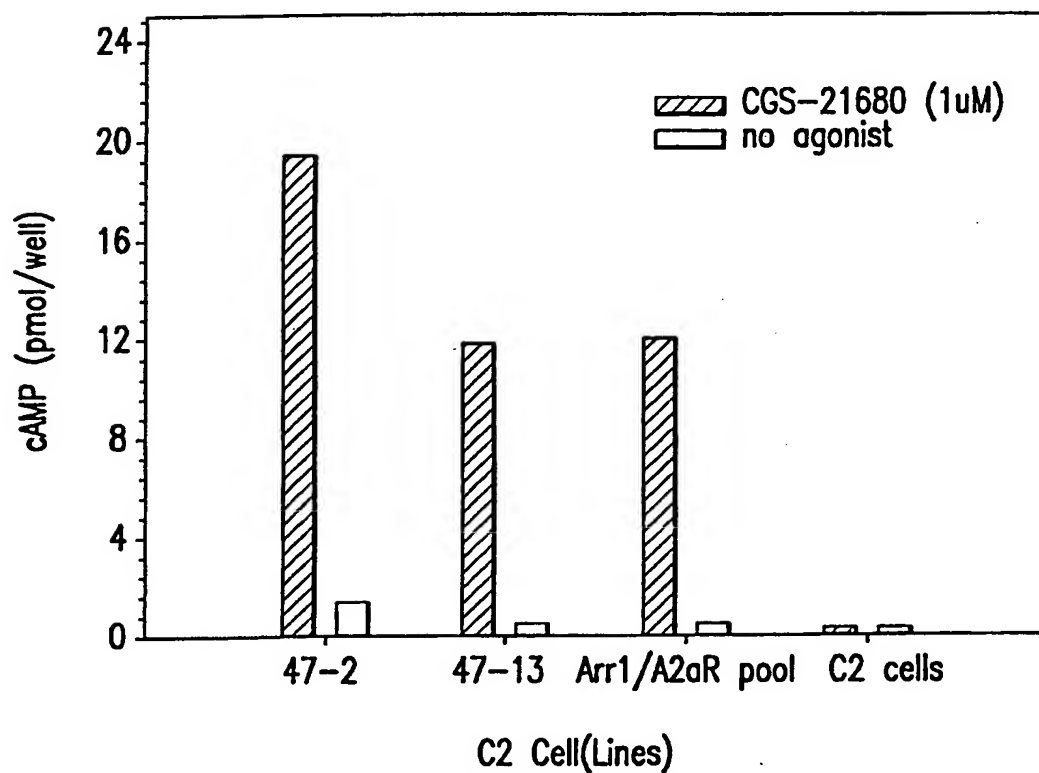


FIG.6

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Agonist Stimulated cAMP Response in Clones or Pools of C2 Cells  
Expressing D1- $\beta$ gal  $\Delta\alpha$  and  $\beta$ Arrestin2- $\beta$ gal  $\Delta\omega$  Fusion Proteins

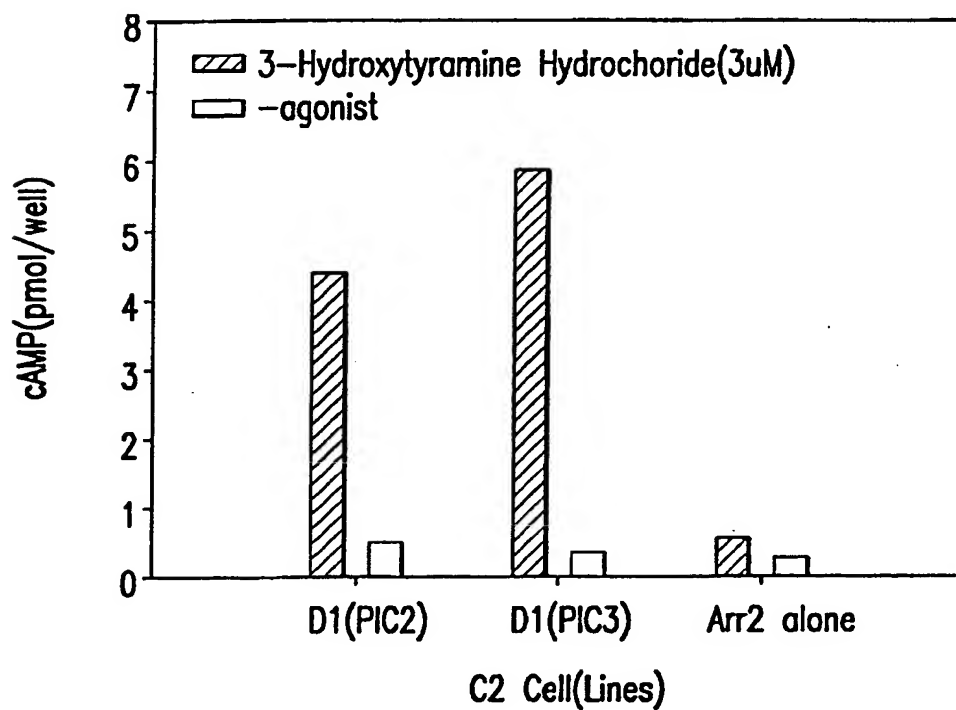


FIG. 7



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$\beta_2$ AR- $\beta$ gal $\Delta\omega$  and  $\beta$ arr2- $\beta$ gal $\Delta\alpha$  Interaction in HEK293  
Clones in Response to Isoproterenol Treatment ( $1\mu\text{M}$ )

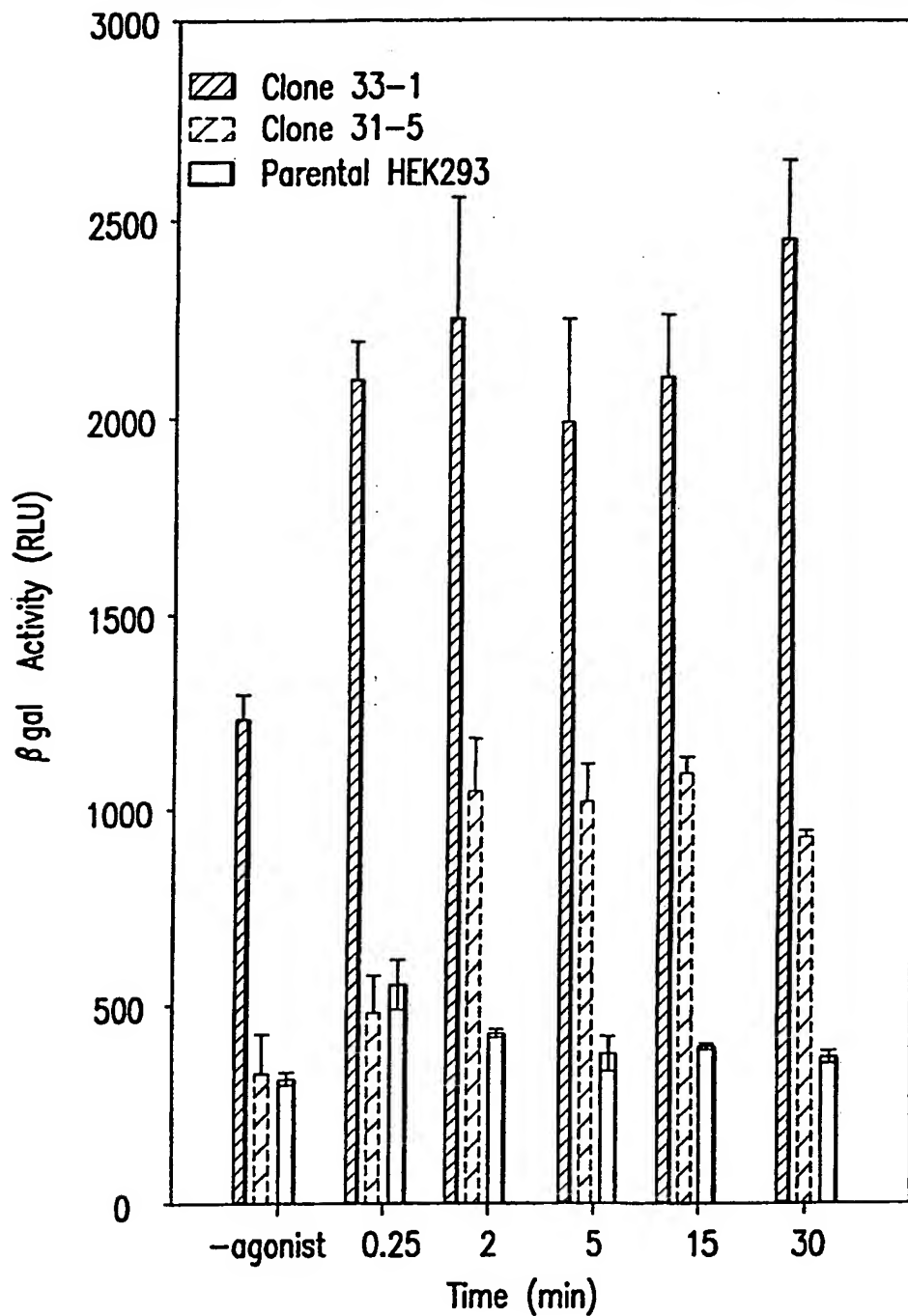


FIG. 8A

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$\beta 2AR-\beta gal\Delta\alpha$  and  $\beta Arr1-\beta gal\Delta\omega$  Interaction in a CHO Pool  
in Response to Isoproterenol Treatment ( $10\mu M$ )

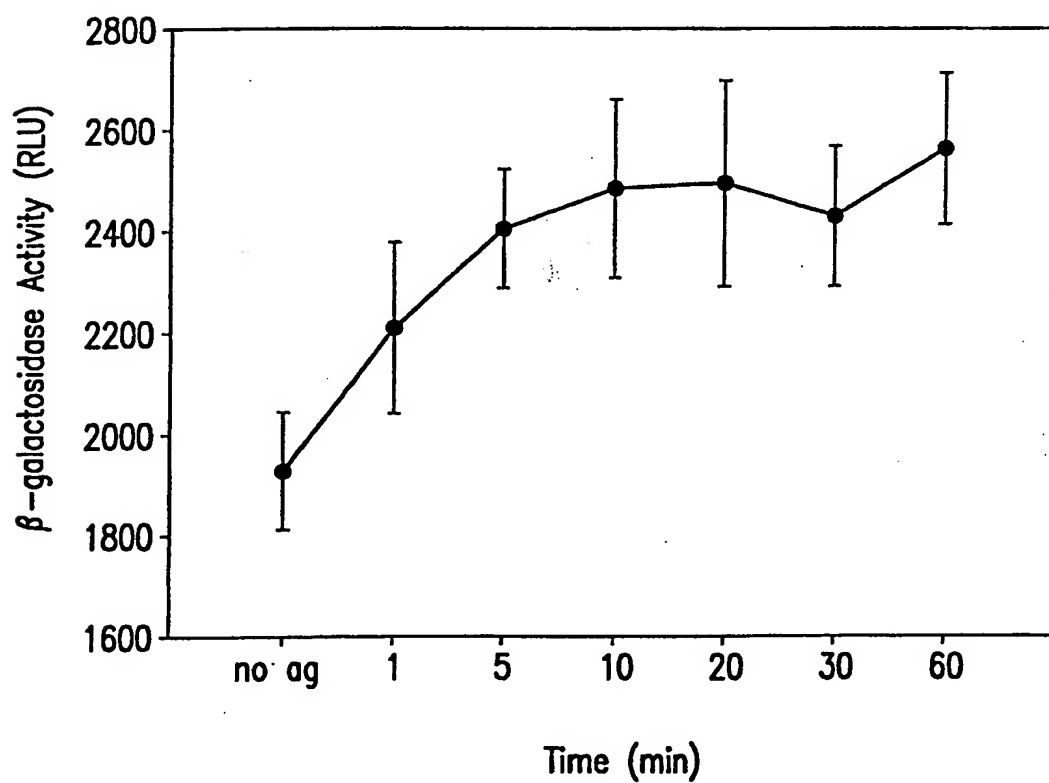


FIG. 8B

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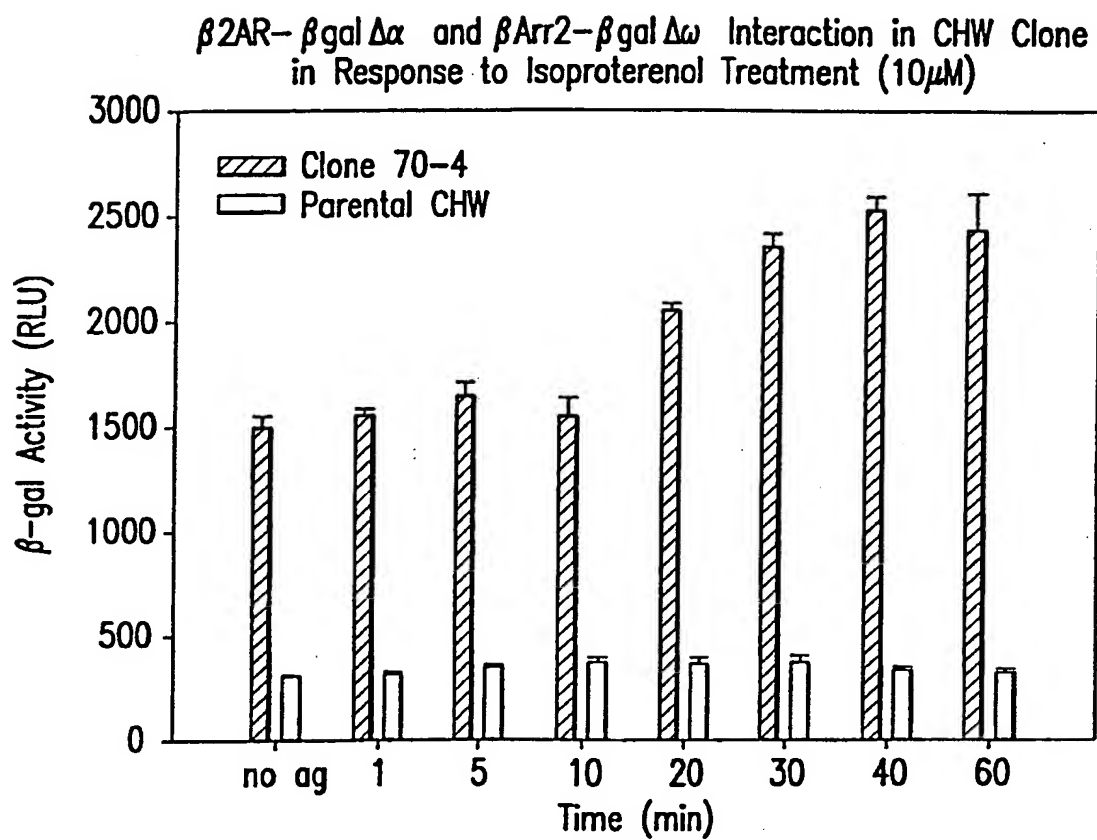


FIG. 8C

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$\beta$ -galactosidase Complementation as a Measurement for  
Adrenergic Receptor Homodimerization in HEK 293 Cells  
Coexpressing  $\beta$ 2AR- $\beta$ gal  $\Delta\alpha$  and  $\beta$ 2AR- $\beta$ gal  $\Delta\omega$ .

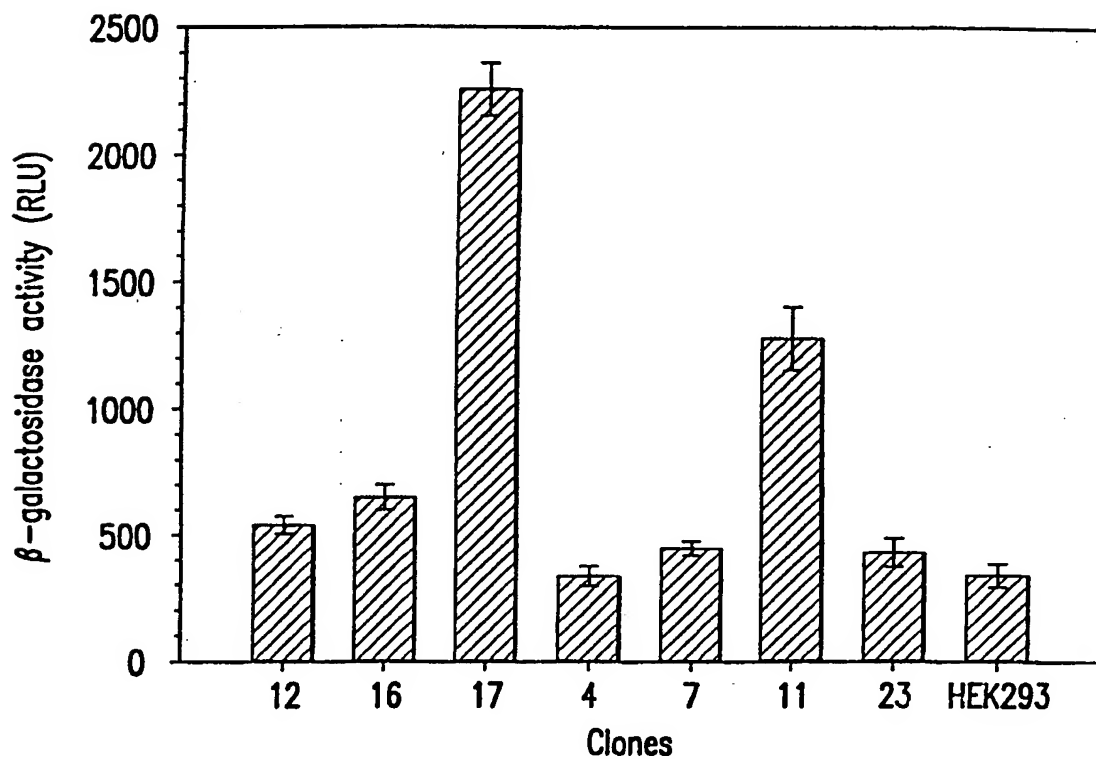


FIG. 9A

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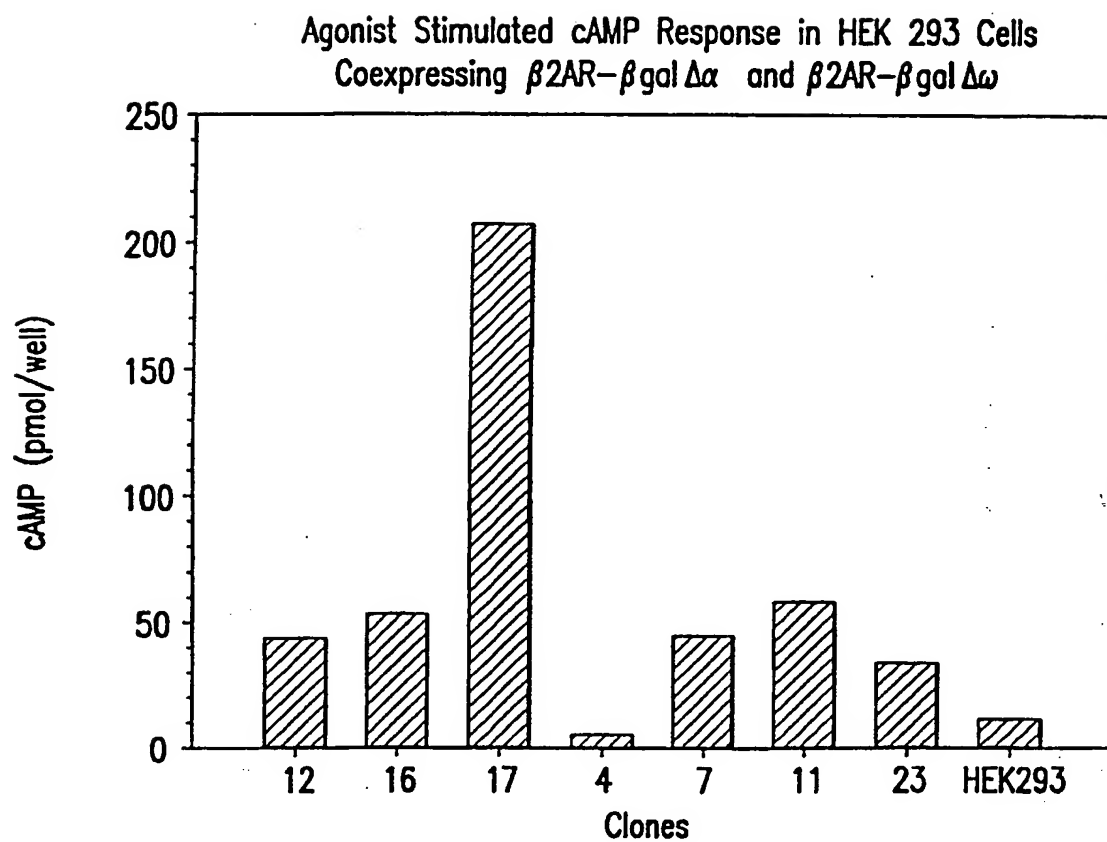


FIG. 9B

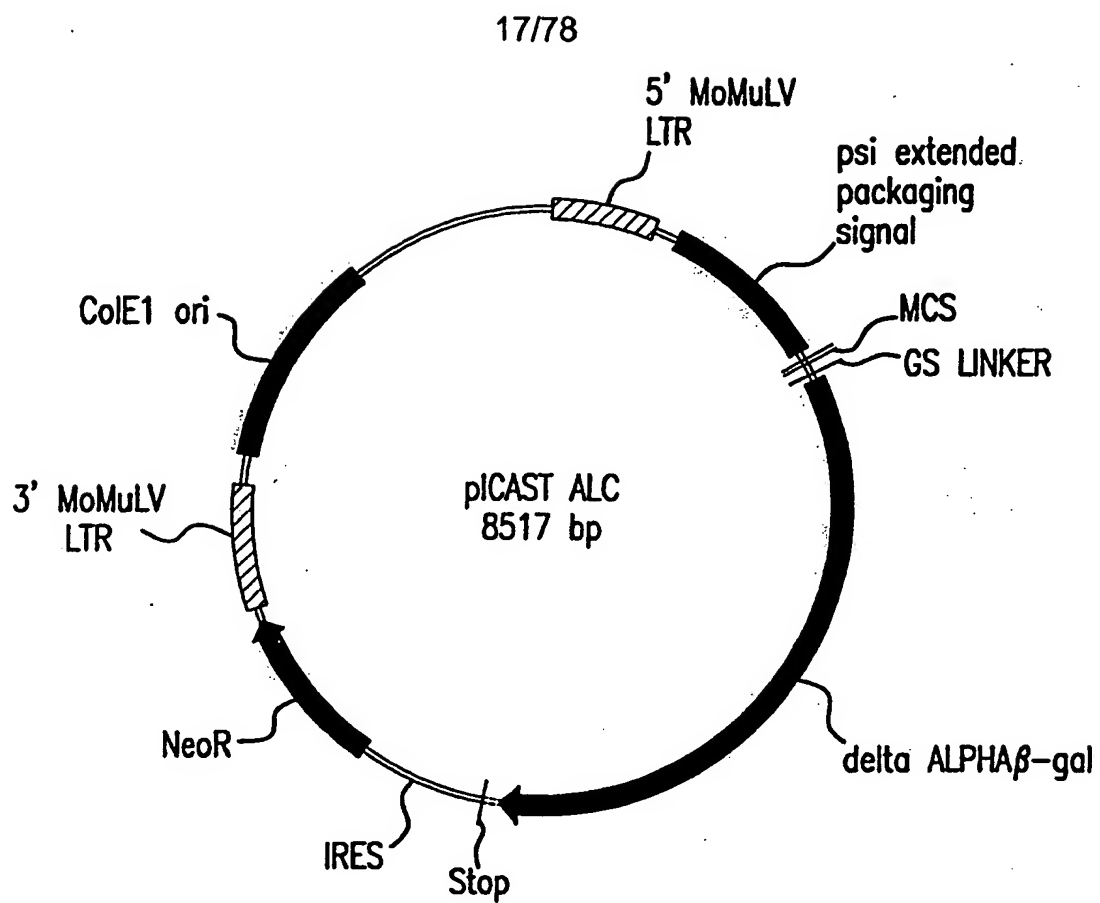


FIG.10A

## pICAST ALC

1 CTGCAGCCTG AATATGGGCC AAACAGGATA TCTGTGGTAA GCAGTTCCTG  
GACGTCGGAC TTATACCCGG TTTGTCCTAT AGACACCATT CGTCAAGGAC

51 CCCC GGCTCA GGGCCAAGAA CAGATGGAAC AGCTGAATAT GGGCCAAACA  
GGGGCCGAGT CCCGGTTCTT GTCTACCTTG TCGACTTATA CCCGGTTTGT

101 GGATATCTGT GGTAAGCAGT TCCTGCCCCG GCTCAGGGCC AAGAACAGAT  
CCTATAGACA CCATTCGTCA AGGACGGGGC CGAGTCCCGG TTCTTGTCTA

151 GGTCCCCAGA TCGGTCCAG CCCTCAGCAG TTTCTAGAGA ACCATCAGAT  
CCAGGGGTCT ACGCCAGGTC GGGAGTCGTC AAAGATCTCT TGGTAGTCTA

201 GTTTCAGGG TGCCCAAGG ACCTGAAATG ACCCTGTGCC TTATTTGAAC  
CAAAGGTCCC ACGGGGTTC TGGACTTTAC TGGGACACGG AATAAACTTG

251 TAACCAATCA GTTCGCTTCT CGCTTCTGTT CGCGCGCTTC TGCTCCCCGA  
ATTGGTTAGT CAAGCGAAGA GCGAAGACAA GCGCGGAAG ACGAGGGGCT

301 GCTCAATAAA AGAGCCCACA ACCCCTCACT CGGGGCGCCA GTCCTCCGAT  
CGAGTTATTT TCTCGGGTGT TGGGGAGTGA GCCCCGCGGT CAGGAGGCTA

351 TGA CTGAGTC GCCCGGTAC CCGTGTATCC AATAAACCTT CTTGCAGTTG  
ACTGACTCAG CGGGCCCATG GGCACATAGG TTATTTGGGA GAACGTCAAC

401 CATCCGACTT GTGGTCTCGC TGTTCCCTGG GAGGGTCTCC TCTGAGTGAT  
GTAGGCTGAA CACCAGAGCG ACAAGGAACC CTCCCAGAGG AGACTCACTA

451 TGA CTACCCG TCAGCGGGGG TCTTTCATTT GGGGGCTCGT CCGGGATCGG  
ACTGATGGGC AGTCGCCCC AGAAAGTAAA CCCCCGAGCA GGCCCTAGCC

501 GAGACCCCTG CCCAGGGACC ACCGACCCAC CACCGGGAGG CAAGCTGGCC  
CTCTGGGGAC GGGTCCCTGG TGGCTGGGTG GTGGCCCTCC GTTCGACCGG

551 AGCAACTTAT CTGTGTCTGT CCGATTGTCT AGTGTCTATG ACTGATTTTA  
TCGTTGAATA GACACAGACA GGCTAACAGA TCACAGATAC TGA CTA AAT

601 TGCGCCTGCG TCGGTACTAG TTAGCTAACT AGCTCTGTAT CTGGCGGACC  
ACGCGGACGC AGCCATGATC AATCGATTGA TCGACACATA GACCGCCTGG

FIG. 10B-1

## pICAST ALC

651 CGTGGTGGAA CTGACGAGTT CTGAACACCC GGCCGCAACC CTGGGAGACG  
GCACCACCTT GACTGCTCAA GACTTGTGGG CCGGCGTTGG GACCCTCTGC

701 TCCCAGGGAC TTTGGGGGCC GTTTTGTGG CCCGACCTGA GGAAGGGAGT  
AGGGTCCCTG AAACCCCGG CAAAACACC GGGCTGGACT CCTTCCCTCA

751 CGATGTGGAA TCCGACCCCG TCAGGATATG TGGTTCTGGT AGGAGACGAG  
GCTACACCTT AGGCTGGGGC AGTCCTATAC ACCAAGACCA TCCTCTGCTC

801 AACCTAAAC AGTTCGCC TCCGTCTGAA TTTTGTCTT CGGTTTGGAA  
TTGGATTTTG TCAAGGGCGG AGGCAGACTT AAAAACGAAA GCCAAACCTT

851 CCGAAGCCGC GCGTCTTGTC TGCTGCAGCA TCGTTCTGTG TTGTCTCTGT  
GGCTTCGGCG CGCAGAACAG ACGACGTCGT AGCAAGACAC AACAGAGACA

901 CTGACTGTGT TTCTGTATTT GTCTGAAAAT TAGGGCCAGA CTGTTACCAC  
GACTGACACA AAGACATAAA CAGACTTTTA ATCCCGGTCT GACAATGGTG

951 TCCCTTAAGT TTGACCTTAG GTAACCTGGAA AGATGTCGAG CGGCTCGCTC  
AGGGAATTCA AACTGGAATC CATTGACCTT TCTACAGCTC GCCGAGCGAG

1001 ACAACCAGTC GGTAGATGTC AAGAAGAGAC GTTGGGTAC CTTCTGCTCT  
TGTTGGTCAG CCATCTACAG TTCTTCTCTG CAACCCAATG GAAGACGAGA

1051 GCAGAATGGC CAACCTTTAA CGTCGGATGG CCGCGAGACG GCACCTTTAA  
CGTCTTACCG GTTGGAAATT GCAGCCTACC GGCCTCTGC CGTGGAAATT

1101 CCGAGACCTC ATCACCAGG TTAAGATCAA GGTCTTTTCA CCTGGCCCGC  
GGCTCTGGAG TAGTGGGTCC AATTCTAGTT CCAGAAAAGT GGACCGGGCG

1151 ATGGACACCC AGACCAGGTC CCCTACATCG TGACCTGGGA AGCCTTGGCT  
TACCTGTGGG TCTGGTCCAG GGGATGTAGC ACTGGACCCT TCGGAACCGA

1201 TTTGACCCCC CTCCCTGGGT CAAGCCCTTT GTACACCCTA AGCCTCCGCC  
AAACTGGGGG GAGGGACCCA GTTCGGGAAA CATGTGGGAT TCGGAGGCGG

1251 TCCTCTTCCT CCATCCGCCC CGTCTCTCCC CTTGAACCT CTCGTTCGA  
AGGAGAAGGA GGTAGGCGGG GCAGAGAGGG GGAACCTGGA GGAGCAAGCT

FIG.10B-2



## pICAST ALC

1301 CCCCgcctcg ATCCTCCCTT TATCCAGCCC TCACTCCTTC TCTAGGCGCC  
GGGGCGGAGC TAGGAGGGAA ATAGGTCGGG AGTGAGGAAG AGATCCGCGG

1351 GGCCGCTCTA GCCCATTAAT ACGACTCACT ATAGGGCGAT TCGAATCAGG  
CCGGCGAGAT CGGGTAATTA TGCTGAGTGA TATCCCGCTA AGCTTAGTCC

1401 CCTTGGCGCG CCGGATCCTT AATTAAGCGC AATTGGGAGG TGGCGGTAGC  
GGAACCGCGC GGCCTAGGAA TTAATTGCGG TTAACCCTCC ACCGCCATCG

+2 M G V I T D S L A V V A R T D  
J-----

1451 CTCGAGATGG GCGTGATTAC GGATTCACTG GCCGTCGTGG CCCGCACCGA  
GAGCTCTACC CGCACTAATG CCTAAGTGAC CGGCAGCACC GGGCGTGGCT

+2 R P S Q Q L R S L N G E W R F A  
-----

1501 TCGCCCTTCC CAACAGTTAC GCAGCCTGAA TGGCGAATGG CGCTTTGCCT  
AGCGGGAAGG GTTGTCAATG CGTCGGACTT ACCGCTTACC GCGAAACGGA

+2 W F P A P E A V P E S W L E C D L  
-----

1551 GGTTTCCGGC ACCAGAAGCG GTGCCGAAA GCTGGCTGGA GTGCGATCTT  
CCAAAGGCCG TGGTCTTCGC CACGGCCTTT CGACCGACCT CACGCTAGAA

+2 P E A D T V V V P S N W Q M H G Y  
-----

1601 CCTGAGGCCG AACTGTGCGT CGTCCCCTCA AACTGGCAGA TGCACGGTTA  
GGACTCCGGC TATGACAGCA GCAGGGGAGT TTGACCGTCT ACGTGCCAAT

+2 D A P I Y T N V T Y P I T V N P  
-----

1651 CGATGCGCCC ATCTACACCA ACGTGACCTA TCCATTACG GTCAATCCGC  
GCTACGCGGG TAGATGTGGT TGCACTGGAT AGGGTAATGC CAGTTAGGCG

+2 P F V P T E N P T G C Y S L T F N  
-----

1701 CGTTTGTTC CACGGAGAAT CCGACGGGTT GTTACTCGCT CACATTTAAT  
GCAAACAAGG GTGCCTCTTA GGCTGCCCAA CAATGAGCGA GTGTAAATTA

FIG.10B-3

## pICAST ALC

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+2     V D E S   W L Q   E G Q   T R I I   F D G  
-----  
1751   GTTGATGAAA GCTGGCTACA GGAAGGCCAG ACGCGAATTA TTTTGTATGG  
       CAACTACTTT CGACCGATGT CCTTCCGGTC TGGCTTAAT AAAAATACC

+2     V N S   A F H L   W C N   G R W   V G Y  
-----  
1801   CGTTAACTCG GCGTTTCATC TGTGGTGCAA CGGGCGCTGG GTCGGTTACG  
       GCAATTGAGC CGCAAAGTAG ACACCACGTT GCCCGCGACC CAGCCAATGC

+2     G Q D S   R L P   S E F D   L S A   F L R  
-----  
1851   GCCAGGACAG TCGTTTGCCG TCTGAATTTG ACCTGAGCGC ATTTTACGCG  
       CGGTCCTGTC AGCAAACGGC AGACTTAAAC TGGACTCGCG TAAAAATGCG

+2     A G E N   R L A   V M V   L R W S   D G S  
-----  
1901   GCCGGAGAAA ACCGCCTCGC GGTGATGGTG CTGCGCTGGA GTGACGGCAG  
       CGGCCTCTTT TGGCGGAGCG CCACTACCAC GACGCGACCT CACTGCCGTC

+2     Y L E   D Q D M   W R M   S G I   F R D  
-----  
1951   TTATCTGGAA GATCAGGATA TGTGGCGGAT GAGCGGCATT TTCCGTGACG  
       AATAGACCTT CTAGTCCTAT ACACCGCCTA CTCGCCGTAA AAGGCACTGC

+2     V S L L   H K P   T T Q I   S D F   H V A  
-----  
2001   TCTCGTTGCT GCATAAACCG ACTACACAAA TCAGCGATTT CCATGTTGCC  
       AGAGCAACGA CGTATTTGGC TGATGTGTTT AGTCGCTAAA GGTACAACGG

+2     T R F N   D D F   S R A   V L E A   E V Q  
-----  
2051   ACTCGCTTTA ATGATGATTT CAGCCGCGCT GTACTGGAGG CTGAAGTTCA  
       TGAGCGAAAT TACTACTAAA GTCGGCGCGA CATGACCTCC GACTTCAAGT

FIG.10B-4

## pICAST ALC

+2     M C G E L R D Y L R V T V S L W  
-----  
2101   GATGTGCGGC GAGTTGCGTG ACTACCTACG GGTAACAGTT TCTTTATGGC  
       CTACACGCCG CTCAACGCAC TGATGGATGC CCATTGTCAA AGAAATACCG

+2     Q G E T Q V A S G T A P F G G E I  
-----  
2151   AGGGTGAAAC GCAGGTCGCC AGCGGCACCG CGCCTTTCGG CGGTGAAATT  
       TCCCACTTTG CGTCCAGCGG TCGCCGTGGC GCGGAAAGCC GCCACTTTAA

+2     I D E R G G Y A D R V T L R L N V  
-----  
2201   ATCGATGAGC GTGGTGTTA TGCCGATCGC GTCACACTAC GTCTGAACGT  
       TAGCTACTCG CACCACCAAT ACGGCTAGCG CAGTGTGATG CAGACTTGCA

+2     E N P K L W S A E I P N L Y R A  
-----  
2251   CGAAAACCCG AAAGTGTGGA GCGCCGAAAT CCCGAATCTC TATCGTGCGG  
       GCTTTTGGGC TTGACACCT CGCGGCTTTA GGGCTTAGAG ATAGCACGCC

+2     V V E L H T A D G T L I E A E A C  
-----  
2301   TGGTTGAACT GCACACCGCC GACGGCACGC TGATTGAAGC AGAAGCCTGC  
       ACCAACTTGA CGTGTGGCGG CTGCCGTGCG ACTAACTTCG TCTTCGGACG

+2     D V G F R E V R I E N G L L L L N  
-----  
2351   GATGTCGGTT TCCGCGAGGT GCGGATTGAA AATGGTCTGC TGCTGCTGAA  
       CTACAGCCAA AGGCGCTCCA CGCCTAACTT TTACCAGACG ACGACGACTT

+2     G K P L L I R G V N R H E H H P  
-----  
2401   CGGCAAGCCG TTGCTGATTC GAGGCGTTAA CCGTCACGAG CATCATCCTC  
       GCCGTTCCGC AACGACTAAG CTCCGCAATT GGCAGTGCTC GTAGTAGGAG

FIG.10B-5

## pICAST ALC

+2    L H G Q V M D E Q T M V Q D I L L  
-----  
2451   TGCATGGTCA GGTCATGGAT GAGCAGACGA TGGTGCAGGA TATCCTGCTG  
      ACGTACCAGT CCAGTACCTA CTCGTCTGCT ACCACGTCCT ATAGGACGAC

+2    M K Q N N F N A V R C S H Y P N H  
-----  
2501   ATGAAGCAGA ACAACTTTAA CGCCGTGCGC TGTTTCGCATT ATCCGAACCA  
      TACTTCGTCT TGTGAAATT GCGGCACGCG ACAAGCGTAA TAGGCTTGGT

+2    P L W Y T L C D R Y G L Y V V D  
-----  
2551   TCCGCTGTGG TACACGCTGT GCGACCGCTA CGGCCTGTAT GTGGTGGATG  
      AGGCGACACC ATGTGCGACA CGCTGGCGAT GCCGGACATA CACCACCTAC

+2    E A N I E T H G M V P M N R L T D  
-----  
2601   AAGCCAATAT TGAAACCCAC GGCATGGTGC CAATGAATCG TCTGACCGAT  
      TTCGGTTATA ACTTTGGGTG CCGTACCACG GTTACTTAGC AGACTGGCTA

+2    D P R W L P A M S E R V T R M V Q  
-----  
2651   GATCCGCGCT GGCTACCGGC GATGAGCGAA CGCGTAACGC GAATGGTGCA  
      CTAGGCGCGA CCGATGGCCG CTA CTGCTT GCGCATTGCG CTTACCACGT

+2    R D R N H P S V I I W S L G N E  
-----  
2701   GCGCGATCGT AATCACCCGA GTGTGATCAT CTGGTCGCTG GGGAAATGAAT  
      CGCGCTAGCA TTAGTGGGCT CACACTAGTA GACCAGCGAC CCCTTACTTA

+2    S G H G A N H D A L Y R W I K S V  
-----  
2751   CAGGCCACGG CGCTAATCAC GACGCGCTGT ATCGCTGGAT CAAATCTGTC  
      GTCCGGTGCC GCGATTAGTG CTGCGCGACA TAGCGACCTA GTTTAGACAG

FIG.10B-6

## pICAST ALC

+2     D P S R P V Q Y E G G G A D T T A  
-----  
2801   GATCCTTCCC GCCCGGTGCA GTATGAAGGC GGC GGAGCCG ACACCACGGC  
       CTAGGAAGGG CGGGCCACGT CATACTTCCG CCGCCTCGGC TGTGGTGCCG

+2     T D I I C P M Y A R V D E D Q P  
-----  
2851   CACCGATATT ATTTGCCCGA TGTACGCGCG CGTGGATGAA GACCAGCCCT  
       GTGGCTATAA TAAACGGGCT ACATGCGCGC GCACCTACTT CTGGTCGGGA

+2     F P A V P K W S I K K W L S L P G  
-----  
2901   TCCCGGCTGT GCCGAAATGG TCCATCAAAA AATGGCTTTC GCTACCTGGA  
       AGGGCCGACA CGGCTTTACC AGGTAGTTTT TTACCGAAAG CGATGGACCT

+2     E T R P L I L C E Y A H A M G N S  
-----  
2951   GAGACGCGCC CGCTGATCCT TTGCGAATAC GCCCAGCGCA TGGGTAACAG  
       CTCTGCGCGG GCGACTAGGA AACGCTTATG CGGGTGCGCT ACCCATTGTC

+2     L G G F A K Y W Q A F R Q Y P R  
-----  
3001   TCTTGGCGGT TTCGCTAAAT ACTGGCAGGC GTTTCGTCAG TATCCCCTT  
       AGAACCGCCA AAGCGATTTA TGACCGTCCG CAAAGCAGTC ATAGGGGCAA

+2     L Q G G F V W D W V D Q S L I K Y  
-----  
3051   TACAGGGCGG CTTCGTCTGG GACTGGGTGG ATCAGTCGCT GATTAAATAT  
       ATGTCCCGCC GAAGCAGACC CTGACCCACC TAGTCAGCGA CTAATTTATA

+2     D E N G N P W S A Y G G D F G D T  
-----  
3101   GATGAAAACG GCAACCCGTG GTCGGCTTAC GCGGGTGATT TTGGCGATAC  
       CTACTTTTGC CGTTGGGCAC CAGCCGAATG CCGCCACTAA AACCGCTATG

FIG.10B-7

## pICAST ALC

+2     P N D R Q F C M N G L V F A D R  
-----  
3151   GCGGAACGAT CGCCAGTTCT GTATGAACGG TCTGGTCTTT GCCGACCGCA  
      CGGCTTGCTA GCGGTCAAGA CATACTTGCC AGACCAGAAA CGGCTGGCGT

+2     T P H P A L T E A K H Q Q Q F F Q  
-----  
3201   CGCCGCATCC AGCGCTGACG GAAGCAAAAC ACCAGCAGCA GTTTTTCCAG  
      GCGGCGTAGG TCGCGACTGC CTTCGTTTG TGGTCGTCGT CAAAAAGTTC

+2     F R L S G Q T I E V T S E Y L F R  
-----  
3251   TTCCGTTTAT CCGGGCAAAC CATCGAAGTG ACCAGCGAAT ACCTGTTCCG  
      AAGGCAAATA GGCCCGTTTG GTAGCTTCAC TGGTCGCTTA TGGACAAGGC

+2     H S D N E L L H W M V A L D G K  
-----  
3301   TCATAGCGAT AACGAGCTCC TGCCTGGAT GGTGGCGCTG GATGGTAAGC  
      AGTATCGCTA TTGCTCGAGG ACGTGACCTA CCACCGCGAC CTACCATTCT

+2     P L A S G E V P L D V A P Q G K Q  
-----  
3351   CGCTGGCAAG CCGTGAAGTG CCTCTGGATG TCGCTCCACA AGGTAAACAG  
      GCGACCGTTC GCCACTTCAC GGAGACCTAC AGCGAGGTGT TCCATTGTCT

+2     L I E L P E L P Q P E S A G Q L W  
-----  
3401   TTGATTGAAC TGCCTGAACT ACCGCAGCCG GAGAGCGCCG GGCAACTCTG  
      AACTAACTTG ACGGACTTGA TGGCGTCGGC CTCTCGCGGC CCGTTGAGAC

+2     L T V R V V Q P N A T A W S E A  
-----  
3451   GCTCACAGTA CGCGTAGTGC AACCGAACGC GACCGCATGG TCAGAAGCCG  
      CGAGTGTCAT GCGCATCACG TTGGCTTGCG CTGGCGTACC AGTCTTCGGC

FIG.10B-8

## pICAST ALC

+2    G H I S   A W Q   Q W R L   A E N   L S V  
-----  
3501   GGCACATCAG CGCCTGGCAG CAGTGGCGTC TGGCGGAAAA CCTCAGTGTG  
      CCGTGTAGTC GCGGACCGTC GTCACCGCAG ACCGCCTTTT GGAGTCACAC

+2    T L P A   A S H   A I P   H L T T   S E M  
-----  
3551   ACGCTCCCCG CCGCGTCCCA CGCCATCCCG CATCTGACCA CCAGCGAAAT  
      TGCGAGGGGC GCGCAGGGT GCGGTAGGGC GTAGACTGGT GGTCGCTTTA

+2    D F C   I E L G   N K R   W Q F   N R Q  
-----  
3601   GGATTTTTGC ATCGAGCTGG GTAATAAGCG TTGGCAATTT AACCGCCAGT  
      CCTAAAAACG TAGCTCGACC CATTATTCGC AACCGTTAAA TTGGCGGTCA

+2    S G F L   S Q M   W I G D   K K Q   L L T  
-----  
3651   CAGGCTTTCT TTCACAGATG TGGATTGGCG ATAAAAACA ACTGCTGACG  
      TGCCGAAAGA AAGTGTCTAC ACCTAACCGC TATTTTTTGT TGACGACTGC

+2    P L R D   Q F T   R A P   L D N D   I G V  
-----  
3701   CCGCTGCGCG ATCAGTTCAC CCGTGCACCG CTGGATAACG ACATTGGCGT  
      GGCGACGCGC TAGTCAAGTG GGCACGTGGC GACCTATTGC TGTAACCGCA

+2    S E A   T R I D   P N A   W V E   R W K  
-----  
3751   AAGTGAAGCG ACCCGCATTG ACCCTAACGC CTGGGTCGAA CGCTGGAAGG  
      TTCATTTCGC TGGGCGTAAC TGGGATTGCG GACCCAGCTT GCGACCTTCC

+2    A A G H   Y Q A   E A A L   L Q C   T A D  
-----  
3801   CGGCGGGCCA TTACCAGGCC GAAGCAGCGT TGTTGCAGTG CACGGCAGAT  
      GCCGCCCGGT AATGGTCCGG CTTCGTCGCA ACAACGTCAC GTGCCGTCTA

FIG.10B-9

## pICAST ALC

+2     T L A D A V L I T T A H A W Q H Q  
-----  
3851    A C A C T T G C T G A T G C G G T G C T G A T T A C G A C C G C T C A C G C G T G G C A G C A T C A  
      T G T G A A C G A C T A C G C C A C G A C T A A T G C T G G C G A G T G C G C A C C G T C G T A G T

+2     G K T L F I S R K T Y R I D G S  
-----  
3901    G G G G A A A A C C T T A T T T A T C A G C C G G A A A C C T A C C G G A T T G A T G G T A G T G  
      C C C C T T T T G G A A T A A A T A G T C G G C C T T T T G G A T G G C C T A A C T A C C A T C A C

+2     G Q M A I T V D V E V A S D T P H  
-----  
3951    G T C A A A T G G C G A T T A C C G T T G A T G T T G A A G T G G C G A G C G A T A C A C C G C A T  
      C A G T T T A C C G C T A A T G G C A A C T A C A A C T T C A C C G C T C G C T A T G T G G C G T A

+2     P A R I G L N C Q L A Q V A E R V  
-----  
4001    C C G G C G C G G A T T G G C C T G A A C T G C C A G C T G G C G C A G G T A G C A G A G C G G G T  
      G G C C G C G C C T A A C C G G A C T T G A C G G T C G A C C G C G T C C A T C G T C T C G C C C A

+2     N W L G L G P Q E N Y P D R L T  
-----  
4051    A A A C T G G C T C G G A T T A G G G C C G C A A G A A A A C T A T C C C G A C C G C C T T A C T G  
      T T T G A C C G A G C C T A A T C C C G G C G T T C T T T T G A T A G G G C T G G C G G A A T G A C

+2     A A C F D R W D L P L S D M Y T P  
-----  
4101    C C G C C T G T T T T G A C C G C T G G G A T C T G C C A T T G T C A G A C A T G T A T A C C C C G  
      G G C G G A C A A A A C T G G C G A C C C T A G A C G G T A A C A G T C T G T A C A T A T G G G G C

+2     T V F P S E N G L R C G T R E L N  
-----  
4151    T A C G T C T T C C C G A G C G A A A A C G G T C T G C G C T G C G G G A C G C G C G A A T T G A A  
      A T G C A G A A G G G C T C G C T T T T G C C A G A C G C G A C G C C C T G C G C G C T T A A C T T

FIG.10B-10



## pICAST ALC

+2     Y G P H Q W R G D F Q F N I S R  
-----  
4201   TTATGGCCCA CACCA GTGGC GCGGCGACTT CCAGTTC AAC ATCAGCCGCT  
       AATACCGGGT GTGGTCACCG CGCCGCTGAA GGTCAAGTTG TAGTCGGCGA

+2     Y S Q Q Q L M E T S H R H L L H A  
-----  
4251   ACAGTCAACA GCAACTGATG GAAACCAGCC ATCGCCATCT GCTGCACGCG  
       TGTCAGTTGT CGTTGACTAC CTTTGGTCGG TAGCGGTAGA CGACGTGCGC

+2     E E G T W L N I D G F H M G I G G  
-----  
4301   GAAGAAGGCA CATGGCTGAA TATCGACGGT TTCCATATGG GGATTGGTGG  
       CTTCTTCCGT GTACCGACTT ATAGCTGGCA AAGGTATACC CCTAACCACC

+2     D D S W S P S V S A E F Q L S A  
-----  
4351   CGACGACTCC TGGAGCCCGT CAGTATCGGC GGAATTCCAG CTGAGCGCCG  
       GCTGCTGAGG ACCTCGGGCA GTCATAGCCG CCTTAAGGTC GACTCGCGGC

+2     G R Y H Y Q L V W C Q K R S D Y K  
-----  
4401   GTCGCTACCA TTACCAGTTG GTCTGGTGTC AAAAAAGATC TGA CTATAAAA  
       CAGCGATGGT AATGGTCAAC CAGACCACAG TTTTCTTAG ACTGATATTT

+2     D E D L D H H H H H H R  
----->  
4451   GATGAGGACC TCGACCATCA TCATCATCAT CACCGGTAAT AATAGGTAGA  
       CTACTCCTGG AGCTGGTAGT AGTAGTAGTA GTGGCCATTA TTATCCATCT

4501   TAAGTACTG ATTAGATGCA TTGATCCCTC GACCAATTCC GGTTATTTTC  
       ATTCACTGAC TAATCTACGT AACTAGGGAG CTGGTTAAGG CCAATAAAAG

4551   CACCATATTG CCGTCTTTTG GCAATGTGAG GGCCCGGAAA CCTGGCCCTG  
       GTGGTATAAC GGCAGAAAAC CGTTACACTC CCGGGCCTTT GGACCGGGAC

FIG.10B-11

## pICAST ALC

4601 TCTTCTTGAC GAGCATTCTT AGGGGTCTTT CCCCTCTCGC CAAAGGAATG  
AGAAGAACTG CTCGTAAGGA TCCCCAGAAA GGGGAGAGCG GTTTCCTTAC

4651 CAAGGTCTGT TGAATGTCGT GAAGGAAGCA GTTCCTCTGG AAGCTTCTTG  
GTTCCAGACA ACTTACAGCA CTTCCTTCGT CAAGGAGACC TTCGAAGAAC

4701 AAGACAAACA ACGTCTGTAG CGACCCTTTG CAGGCAGCGG AACCCCCAC  
TTCTGTTTGT TGCAGACATC GCTGGGAAAC GTCCGTCGCC TTGGGGGGTG

4751 CTGGCGACAG GTGCCTCTGC GGCCAAAAGC CACGTGTATA AGATACACCT  
GACCGCTGTC CACGGAGACG CCGGTTTTCG GTGCACATAT TCTATGTGGA

4801 GCAAAGGCGG CACAACCCCA GTGCCACGTT GTGAGTTGGA TAGTTGTGGA  
CGTTTCCGCC GTGTTGGGGT CACGGTGCAA CACTCAACCT ATCAACACCT

4851 AAGAGTCAAA TGGCTCTCCT CAAGCGTATT CAACAAGGGG CTGAAGGATG  
TTCTCAGTTT ACCGAGAGGA GTTCGCATAA GTTGTTCCCC GACTTCCTAC

4901 CCCAGAAGGT ACCCCATTGT ATGGGATCTG ATCTGGGGCC TCGGTGCACA  
GGGTCTTCCA TGGGGTAACA TACCCTAGAC TAGACCCCGG AGCCACGTGT

4951 TGCTTTACAT GTGTTTAGTC GAGGTAAAA AACGTCTAGG CCCCCGAAC  
ACGAAATGTA CACAAATCAG CTCCAATTTT TTGCAGATCC GGGGGGCTTG

5001 CACGGGGACG TGGTTTTCTT TTGAAAAACA CGATGATAAT ACCATGATTG  
  
GTGCCCCTGC ACCAAAAGGA AACTTTTTGT GCTACTATTA TGGTACTAAC

5051 AACAAGATGG ATTGCACGCA GGTTCCTCCG CCGCTTGGGT GGAGAGGCTA  
TTGTTCTACC TAACGTGCGT CCAAGAGGCC GCGGAACCCA CCTCTCCGAT

5101 TTCGGCTATG ACTGGGCACA ACAGACAATC GGCTGCTCTG ATGCCGCCGT  
AAGCCGATAC TGACCCGTGT TGTCTGTTAG CCGACGAGAC TACGGCGGCA

5151 GTTCCGGCTG TCAGCGCAGG GCGCCCCGGT TCTTTTGTG AAGACCGACC  
CAAGGCCGAC AGTCGCGTCC CCGCGGGCCA AGAAAAACAG TTCTGGCTGG

FIG. 10B-12

## pICAST ALC

5201 TGTCCGGTGC CCTGAATGAA CTGCAGGACG AGGCAGCGCG GCTATCGTGG  
ACAGGCCACG GGACTTACTT GACGTCCTGC TCCGTCGCGC CGATAGCACC

5251 CTGGCCACGA CGGGCGTTCC TTGCGCAGCT GTGCTCGACG TTGTCACTGA  
GACCGGTGCT GCCCGCAAGG AACGCGTCGA CACGAGCTGC AACAGTGACT

5301 AGCGGGAAGG GACTGGCTGC TATTGGGCGA AGTGCCGGGG CAGGATCTCC  
TCGCCCTTCC CTGACCGACG ATAACCCGCT TCACGGCCCC GTCCTAGAGG

5351 TGTCATCTCA CCTTGCTCCT GCCGAGAAAG TATCCATCAT GGCTGATGCA  
ACAGTAGAGT GGAACGAGGA CGGCTCTTTC ATAGGTAGTA CCGACTACGT

5401 ATGCGGCGGC TGCATACGCT TGATCCGGCT ACCTGCCCAT TCGACCACCA  
TACGCCGCCG ACGTATGCGA ACTAGGCCGA TGGACGGGTA AGCTGGTGGT

5451 AGCGAAACAT CGCATCGAGC GAGCACGTAC TCGGATGGAA GCCGGTCTTG  
TCGCTTTGTA GCGTAGCTCG CTCGTGCATG AGCCTACCTT CGGCCAGAAC

5501 TCGATCAGGA TGATCTGGAC GAAGAGCATC AGGGGCTCGC GCCAGCCGAA  
AGTAGTCCT ACTAGACCTG CTTCTCGTAG TCCCGAGCG CGGTCGGCTT

5551 CTGTTGCGCA GGCTCAAGGC GCGCATGCCC GACGGCGAGG ATCTCGTCGT  
GACAAGCGGT CCGAGTTCCG CGCGTACGGG CTGCCGCTCC TAGAGCAGCA

5601 GACCCATGGC GATGCCTGCT TGCCGAATAT CATGGTGGAA AATGGCCGCT  
CTGGGTACCG CTACGGACGA ACGGCTTATA GTACCACCTT TTACCGGCGA

5651 TTTCTGGATT CATCGACTGT GGCCGGCTGG GTGTGGCGGA CCGCTATCAG  
AAAGACCTAA GTAGCTGACA CCGGCCGACC CACACCGCCT GGCGATAGTC

5701 GACATAGCGT TGGTACCCG TGATATTGCT GAAGAGCTTG GCGGCGAATG  
CTGTATCGCA ACCGATGGGC ACTATAACGA CTTCTCGAAC CGCCGCTTAC

5751 GGCTGACCGC TTCCTCGTGC TTTACGGTAT CGCCGCTCCC GATTGCGAGC  
CCGACTGGCG AAGGAGCACG AAATGCCATA GCGGCGAGGG CTAAGCGTCG

FIG.10B-13

## pICAST ALC

5801 GCATCGCCTT CTATCGCCTT CTTGACGAGT TCTTCTGAGC GGGACTCTGG  
CGTAGCGGAA GATAGCGGAA GAACTGCTCA AGAAGACTCG CCCTGAGACC

5851 GGTTCGCATC GATAAAATAA AAGATTTTAT TTAGTCTCCA GAAAAAGGGG  
CCAAGCGTAG CTATTTTATT TTCTAAAATA AATCAGAGGT CTTTTTCCCC

5901 GGAATGAAAG ACCCCACCTG TAGGTTTGGC AAGCTAGCTT AAGTAACGCC  
CCTTACTTTC TGGGGTGGAC ATCCAAACCG TTCGATCGAA TTCATTGCGG

5951 ATTTTGCAAG GCATGGAAAA ATACATAACT GAGAATAGAG AAGTTCAGAT  
TAAACGTTT CGTACCTTTT TATGTATTGA CTCTTATCTC TTCAAGTCTA

6001 CAAGGTCAGG AACAGATGGA ACAGCTGAAT ATGGGCCAAA CAGGATATCT  
GTTCCAGTCC TTGTCTACCT TGTCGACTTA TACCCGGTTT GTCCTATAGA

6051 GTGGTAAGCA GTTCCTGCCC CGGCTCAGGG CCAAGAACAG ATGGAACAGC  
CACCATTCTG CAAGGACGGG GCCGAGTCCC GGTTCCTGTC TACCTTGTCG

6101 TGAATATGGG CCAAACAGGA TATCTGTGGT AAGCAGTTCC TGCCCCGGCT  
ACTTATACCC GGTTCCTGCT ATAGACACCA TTCGTCAAGG ACGGGGCCGA

6151 CAGGGCCAAG AACAGATGGT CCCAGATGC GGTCCAGCCC TCAGCAGTTT  
GTCCCGGTTT TTGTCTACCA GGGGTCTACG CCAGGTCGGG AGTCGTCAAA

6201 CTAGAGAACC ATCAGATGTT TCCAGGGTGC CCCAAGGACC TGAAATGACC  
GATCTCTTGG TAGTCTACAA AGGTCCCACG GGGTTCCTGG ACTTTACTGG

6251 CTGTGCCTTA TTTGAACTAA CCAATCAGTT CGCTTCTCGC TTCTGTTTCG  
GACACGGAAT AAACCTTGATT GGTTAGTCAA GCGAAGAGCG AAGACAAGCG

6301 GCGCTTCTGC TCCCCGAGCT CAATAAAAGA GCCCACAACC CCTCACTCGG  
CGCGAAGACG AGGGGCTCGA GTTATTTTCT CGGGTGTTGG GGAGTGAGCC

6351 GGCGCCAGTC CTCCGATTGA CTGAGTCGCC CGGGTACCCG TGTATCCAAT  
CCGCGGTCAG GAGGCTAACT GACTCAGCGG GCCCATGGGC ACATAGGTTA

FIG.10B-14

## pICAST ALC

6401 AAACCCTCTT GCAGTTGCAT CCGACTTGTG GTCTCGCTGT TCCTTGGGAG  
TTTGGGAGAA CGTCAACGTA GGCTGAACAC CAGAGCGACA AGGAACCCTC

6451 GGTCTCCTCT GAGTGATTGA CTACCCGTCA GCGGGGGTCT TTCATTGATG  
CCAGAGGAGA CTCACTAACT GATGGGCAGT CGCCCCAGA AAGTAAGTAC

6501 CAGCATGTAT CAAAATTAAT TTGGTTTTTT TTCTTAAGTA TTTACATTAA  
GTCGTACATA GTTTTAATTA AACCAAAAAA AAGAATTCAT AAATGTAATT

6551 ATGGCCATAG TTGCATTAAT GAATCGGCCA ACGCGCGGGG AGAGGCGGTT  
TACCGGTATC AACGTAATTA CTTAGCCGGT TCGCGGCCCC TCTCCGCCAA

6601 TGC GTATTGG CGCTCTTCCG CTTCTCGCT CACTGACTCG CTGCGCTCGG  
ACGCATAACC GCGAGAAGGC GAAGGAGCGA GTGACTGAGC GACGCGAGCC

6651 TCGTTCGGCT GCGGCGAGCG GTATCAGCTC ACTCAAAGGC GGTAATACGG  
AGCAAGCCGA CGCCGCTCGC CATAGTCGAG TGAGTTTCCG CCATTATGCC

FIG.10B-15

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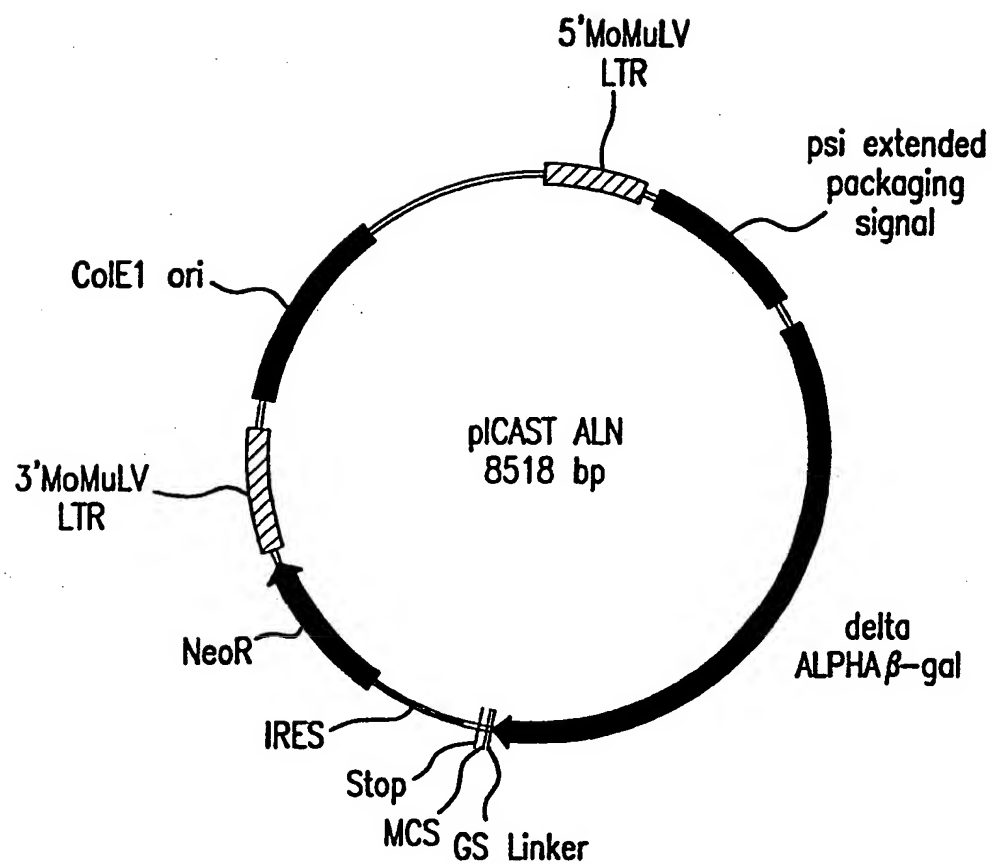


FIG.11A

## pICAST ALN

CTGCAGCCTG AATATGGGCC AACAGGATA TCTGTGGTAA GCAGTTCCTG CCCC GGCTCA	60
GACGTCGGAC TTATACCCGG TTTGTCCTAT AGACACCATT CGTCAAGGAC GGGGCCGAGT	60
GGGCCAAGAA CAGATGGAAC AGCTGAATAT GGGCCAAACA GGATATCTGT GGTAAGCAGT	120
CCCGGTTCTT GTCTACCTTG TCGACTTATA CCCGGTTTGT CCTATAGACA CCATTCGTCA	120
TCCTGCCCCG GCTCAGGGCC AAGAACAGAT GGTCCCCAGA TCGGGTCCAG CCCTCAGCAG	180
AGGACGGGGC CGAGTCCCGG TTCTTGCTA CCAGGGGTCT ACGCCAGGTC GGGAGTCGTC	180
TTTCTAGAGA ACCATCAGAT GTTTCAGGG TGCCCCAAGG ACCTGAAATG ACCCTGTGCC	240
AAAGATCTCT TGGTAGTCTA CAAAGGTCCC ACGGGGTTC TGGACTTTAC TGGGACACGG	240
TTATTTGAAC TAACCAATCA GTTCGCTTCT CGCTTCTGTT CGCGCGCTTC TGCTCCCCGA	300
AATAAACTTG ATTGGTTAGT CAAGCGAAGA GCGAAGACAA GCGCGCGAAG ACGAGGGGCT	300
GCTCAATAAA AGAGCCCACA ACCCGTCACT CGGGGCGCCA GTCCTCCGAT TGA CTGAGTC	360
CGAGTTATTT TCTCGGGTGT TGGGGAGTGA GCCCGCGGT CAGGAGGCTA ACTGACTCAG	360
GCCCGGGTAC CCGTGTATCC AATAAACCT CTTGCAGTTG CATCCGACTT GTGGTCTCGC	420
CGGGCCCATG GGCACATAGG TTATTTGGGA GAACGTCAAC GTAGGCTGAA CACCAGAGCG	420
TGTTCTTG GAGGGTCTCC TCTGAGTGAT TGA CTACCCG TCAGCGGGGG TCTTTCATTT	480
ACAAGGAACC CTCCAGAGG AGACTACTA ACTGATGGGC AGTCGCCCCC AGAAAGTAAA	480
GGGGGCTCGT CCGGATCGG GAGACCCCTG CCCAGGGACC ACCGACCCAC CACCGGGAGG	540
CCCCGAGCA GGCCCTAGCC CTCTGGGGAC GGGTCCCTGG TGGCTGGGTG GTGGCCCTCC	540
CAAGCTGGCC AGCAACTTAT CTGTGTCTGT CCGATTGTCT AGTGTCTATG ACTGATTTTA	600
GTTGACCGG TCGTTGAATA GACACAGACA GGCTAACAGA TCACAGATAC TGA CTAAAAT	600
TGCGCCTGCG TCGGTACTAG TTAGCTAACT AGCTCTGTAT CTGGCGGACC CGTGGTGGAA	660
ACGCGGACGC AGCCATGATC AATCGATTGA TCGAGACATA GACCGCTGG GCACCACCTT	660
CTGACGAGTT CTGAACACCC GGCCGCAACC CTGGGAGACG TCCCAGGGAC TTTGGGGGCC	720
GACTGCTCAA GACTTGTGGG CCGGCGTTGG GACCCTCTGC AGGGTCCCTG AAACCCCGG	720
GTTTTTGTGG CCCGACCTGA GGAAGGGAGT CGATGTGGAA TCCGACCCCG TCAGGATATG	780
CAAAAACACC GGGCTGGACT CCTTCCTCA GCTACACCTT AGGCTGGGGC AGTCCTATAC	780

FIG. 11B-1

## pICAST ALN

TGGTTCTGGT AGGAGACGAG AACCTAAAC AGTCCCGCC TCCGTCTGAA TTTTGTCTT	840
ACCAAGACCA TCCTCTGCTC TTGGATTTTG TCAAGGGCGG AGGCAGACTT AAAACGAAA	840
CGGTTTGGAA CCGAAGCCGC GCGTCTTGTC TGCTGCAGCA TCGTTCTGTG TTGTCTCTGT	900
GCCAAACCTT GGCTTCGGCG CGCAGAACAG ACGACGTCGT AGCAAGACAC AACAGAGACA	900
CTGACTGTGT TTCTGTATTT GTCTGAAAT TAGGGCCAGA CTGTTACCAC TCCCTTAAGT	960
GACTGACACA AAGACATAAA CAGACTTTTA ATCCCGGTCT GACAATGGTG AGGGAATTCA	960
TTGACCTTAG GTAACGGAA AGATGTCGAG CGGCTCGCTC ACAACCAAGTC GGTAGATGTC	1020
AACTGGAATC CATTGACCTT TCTACAGCTC GCCGAGCGAG TGTGGTCAG CCATCTACAG	1020
AAGAAGAGAC GTTGGGTAC CTTCTGCTCT GCAGAATGGC CAACCTTTAA CGTCGGATGG	1080
TTCTTCTCTG CAACCCAATG GAAGACGAGA CGTCTTACCG GTTGGAAATT GCAGCCTACC	1080
CCGCGAGACG GCACCTTTAA CCGAGACCTC ATCACCAGG TTAAGATCAA GGTCTTTTCA	1140
GGCGCTCTGC CGTGGAAATT GGCTCTGGAG TAGTGGGTCC AATTCTAGTT CCAGAAAAGT	1140
CCTGGCCCGC ATGGACACCC AGACCAGGTC CCCTACATCG TGACCTGGGA AGCCTTGGCT	1200
GGACCGGGCG TACCTGTGGG TCTGGTCCAG GGGATGTAGC ACTGGACCCT TCGBAACCBA	1200
TTTGACCCCC CTCCCTGGGT CAAGCCCTTT GTACACCCTA AGCCTCCGCC TCCTCTTCCT	1260
AACTGGGGG GAGGGACCCA GTTCGGGAAA CATGTGGGAT TCGGAGGCGG AGGAGAAGGA	1260
CCATCCGCCC CGTCTCTCCC CTTGAACCT CCTCGTTCGA CCCCCTCTCG ATCCTCCCTT	1320
GGTAGGCGGG GCAGAGAGGG GGAACCTTGA GGAGCAAGCT GGGGCGGAGC TAGGAGGGAA	1320
TATCCAGCCC TCACTCCTTC TCTAGGCGCC GGCCGCTCTA GCCCATTAAAT ACGACTCACT	1380
ATAGGTCGGG AGTGAGGAAG AGATCCGCGG CCGGCGAGAT CGGGTAATTA TGCTGAGTGA	1380
ATAGGGCGAT TCGAACACCA TGCACCATCA TCATCATCAC GTCGACTATA AAGATGAGGA	1440
TATCCCGCTA AGCTTGTTGT ACGTGGTAGT AGTAGTAGTG CAGCTGATAT TTCTACTCCT	1440
CCTCGAGATG GGCCTGATTA CGGATTCATC GGCCGTCGTG GCCCGCACCG ATCGCCCTTC	1500
GGAGCTCTAC CCGCACTAAT GCCTAAGTGA CCGGCGAGC CGGGCGTGGC TAGCGGGAAG	1500
CCAACAGTTA CGCAGCCTGA ATGGCGAATG GCGCTTTGCC TGGTTTCCGG CACCAGAAGC	1560
GGTTGTCAAT GCGTCGACT TACCGCTTAC CGCGAAACGG ACCAAAGGCC GTGGTCTTCG	1560

FIG. 11B-2



## pICAST ALN

GGTGCCGGAA AGCTGGCTGG AGTGCGATCT TCCTGAGGCC GATACTGTCTG TCGTCCCCTC	1620
CCACGGCCTT TCGACCGACC TCACGCTAGA AGGACTCCGG CTATGACAGC AGCAGGGGAG	1620
AAACTGGCAG ATGCACGGTT ACGATGCGCC CATCTACACC AACGTGACCT ATCCCATTAC	1680
TTTGACCGTC TACGTGCCAA TGCTACGCGG GTAGATGTGG TTGCACTGGA TAGGGTAATG	1680
GGTCAATCCG CCGTTTGTTC CCACGGAGAA TCCGACGGGT TGTTACTCGC TCACATTTAA	1740
CCAGTTAGGC GGCAAACAAG GGTGCCTCTT AGGCTGCCCA ACAATGAGCG AGTGTAATT	1740
TGTTGATGAA AGCTGGCTAC AGGAAGGCCA GACGCGAATT ATTTTGTATG GCGTTAACTC	1800
ACAACTACTT TCGACCGATG TCCTTCCGGT CTGCGCTTAA TAAAACTAC CGCAATTGAG	1800
GGCGTTTCAT CTGTGGTGCA ACGGGCGCTG GGTGCGTTAC GGCCAGGACA GTCGTTTGCC	1860
CCGCAAAGTA GACACCACGT TGCCCGCGAC CCAGCCAATG CCGGTCCTGT CAGCAAACGG	1860
GTCTGAATTT GACCTGAGCG CATTTTTACG CGCCGGAGAA AACC GCCTCG CCGTGATGGT	1920
CAGACTTAAA CTGGACTCGC GTAAAAATGC GCGGCCTCTT TTGGCGGAGC GCCACTACCA	1920
GCTGGGCTGG AGTGACGGCA GTTATCTGGA AGATCAGGAT ATGTGGCGGA TGAGCGGCAT	1980
CGACGCGACC TCACTGCCGT CAATAGACCT TCTAGTCCTA TACACCGCCT ACTCGCCGTA	1980
TTTCCGTGAC GTCTCGTTGC TGCATAAACC GACTACACAA ATCAGCGATT TCCATGTTGC	2040
AAAGGCACTG CAGAGCAACG ACGTATTTGG CTGATGTGTT TAGTCGCTAA AGGTACAACG	2040
CACTCGCTTT AATGATGATT RCAGCCGCGC TGTA CTGGAG GCTGAAGTTC AGATGTGCGG	2100
GTGAGCGAAA TTACTACTAA AGTCGGCGCG ACATGACCTC CGACTTCAAG TCTACACGCC	2100
CGAGTTGCGT GACTACCTAC GGGTAACAGT TTCTTTATGG CAGGGTGAAA CGCAGGTCGC	2160
GCTCAACGCA CTGATGGATG CCCATTGTCA AAGAAATACC GTCCCACTTT GCGTCCAGCG	2160
CAGCGGCACC GCGCCTTTCTG GCGGTGAAAT TATCGATGAG CGTGGTGGTT ATGCCGATCG	2220
GTGCGCGTGG CGCGGAAAGC CGCCACTTTA ATAGCTACTC GCACCACCAA TACGGCTAGC	2220
CGTCACACTA CGTCTGAACG TCGAAAACCC GAAACTGTGG AGCGCCGAAA TCCCGAATCT	2280
GCAGTGTGAT GCAGACTTGC AGCTTTTGGG CTTTGACACC TCGCGGCTTT AGGGCTTAGA	2280
CTATCGTGCG GTGGTTGAAC TGCACACCGC CGACGGCACG CTGATTGAAG CAGAAGCCTG	2340
GATAGCACGC CACCAACTTG ACGTGTGGCG GCTGCCGTGC GACTAACTTC GTCTTCGGAC	2340

FIG. 11B-3

## pICAST ALN

CGATGTCGGT TTCCGCGAGG TGC GGATTGA AAATGGTCTG CTGCTGCTGA ACGGCAAGCC	2400
GCTACAGCCA AAGGCGCTCC ACGCCTAACT TTTACCAGAC GACGACGACT TGCCGTTCCG	2400
GTTGCTGATT CGAGGCGTTA ACCGTCACGA GCATCATCCT CTGCATGGTC AGGTCATGGA	2460
CAACGACTAA GCTCCGCAAT TGGCAGTGCT CGTAGTAGGA GACGTACCAG TCCAGTACCT	2460
TGAGCAGACG ATGGTGCAGG ATATCCTGCT GATGAAGCAG AACAACTTTA ACGCCGTGCG	2520
ACTCGTCTGC TACCACGTCC TATAGGACGA CTACTTCGTC TTGTTGAAAT TGCGGCACGC	2520
CTGTTTCGCAT TATCCGAACC ATCCGCTGTG GTACACGCTG TGCGACCGCT ACGGCCTGTA	2580
GACAAGCGTA ATAGGCTTGG TAGGCGACAC CATGTGCGAC ACGCTGGCGA TGCCGGACAT	2580
TGTGGTGGAT GAAGCCAATA TTGAAACCCA CGGCATGGTG CCAATGAATC GTCTGACCGA	2640
ACACCACCTA CTTCGGTTAT AACTTTGGGT GCCGTACCAC GGTTACTTAG CAGACTGGCT	2640
TGATCCGCGC TGGCTACCGG CGATGAGCGA ACGCGTAACG CGAATGGTGC AGCGCGATCG	2700
ACTAGGCGCG ACCGATGGCC GCTACTCGCT TCGCATTGC GCTTACCACG TCGCGCTAGC	2700
TAATCACCCG AGTGTGATCA TCTGGTCGCT GGGGAATGAA TCAGGCCACG GCGCTAATCA	2760
ATTAGTGGGC TCACACTAGT AGACCAGCGA CCCCTTACTT AGTCCGGTGC CGCGATTAGT	2760
CGACGCGCTG TATCGCTGGA TCAAATCTGT CGATCCTTCC CGCCCGGTGC AGTATGAAGG	2820
GCTGCGCGAC ATAGCGACCT AGTTTAGACA GCTAGGAAGG GCGGGCCACG TCATACTTCC	2820
CGGCGGAGCC GACACCACGG CCACCGATAT TATTTGCCCG ATGTACGCGC GCGTGGATGA	2880
GCCGCCTCGG CTGTGGTGCC GGTGGCTATA ATAAACGGGC TACATGCGCG CGCACCTACT	2880
AGACCAGCCC TTCCCGGCTG TGCCGAAATG GTCCATCAAA AAATGGCTTT CGCTACCTGG	2940
TCTGGTCGGG AAGGGCCGAC ACGGCTTTAC CAGGTAGTTT TTTACCGAAA GCGATGGACC	2940
AGAGACGCGC CCGCTGATCC TTTGCGAATA CGCCACGCG ATGGGTAACA GTCTTGGCGG	3000
TCTCTGCGCG GCGACTAGG AAACGCTTAT GCGGGTGC GC TACCCATTGT CAGAACCGCC	3000
TTTCGCTAAA TACTGGCAGG CGTTTCGTCA GTATCCCCGT TTACAGGGCG GCTTCGTCTG	3060
AAAGCGATTT ATGACCGTCC GCAAAGCAGT CATAGGGGCA AATGTCCCGC CGAAGCAGAC	3060
GGA CTGGGTG GATCAGTCGC TGATTAAATA TGATGAAAAC GGCAACCCGT GGTCGGCTTA	3120
CCTGACCCAC CTAGTCAGCG ACTAATTTAT ACTACTTTTG CCGTTGGGCA CCAGCCGAAT	3120

FIG. 11B-4

## pICAST ALN

CGGCGGTGAT TTTGGCGATA CGCCGAACGA TCGCCAGTTC TGTATGAACG GTCTGGTCTT	3180
GCCGCCACTA AAACCGCTAT GCGGCTTGCT AGCGGTCAAG ACATACTTGC CAGACCAGAA	3180
TGCCGACCGC ACGCCGCATC CAGCGCTGAC GGAAGCAAAA CACCAGCAGC AGTTTTTCCA	3240
ACGGCTGGCG TCGGGCGTAG GTCGCGACTG CCTTCGTTTT GTGGTCGTCG TCAAAAAGGT	3240
GTTCCGTTTA TCCGGGCAAA CCATCGAAGT GACCAGCGAA TACCTGTTCC GTCATAGCGA	3300
CAAGGCAAAT AGGCCCGTTT GGTAGCTTCA CTGGTCGCTT ATGGACAAGG CAGTATCGCT	3300
TAACGAGCTC CTGCACTGGA TGGTGGCGCT GGATGGTAAG CCGCTGGCAA GCGGTGAAGT	3360
ATTGCTCGAG GACGTGACCT ACCACCGCGA CCTACCATTG GCGGACCGTT CGCCACTTCA	3360
GCCTCTGGAT GTCGCTCCAC AAGGTAAACA GTTGATTGAA CTGCCTGAAC TACCGCAGCC	3420
CGGAGACCTA CAGCGAGGTG TTCCATTTGT CAACTAATT GACGGACTTG ATGGCGTCGG	3420
GGAGAGCGCC GGGCAACTCT GGCTCACAGT ACGCGTAGTG CAACCGAACG CGACCGCATG	3480
CCTCTCGCGG CCCGTTGAGA CCGAGTGTCA TGCGCATCAC GTTGGCTTGC GCTGGCGTAC	3480
GTCAGAAGCC GGGCACATCA GCGCCTGGCA GCAGTGGCGT CTGGCGGAAA ACCTCAGTGT	3540
CAGTCTTCGG CCCGTGTAGT CGCGGACCGT CGTCACCGCA GACCGCCTTT TGGAGTCACA	3540
GACGCTCCCC GCCGCTCCC ACGCCATCCC GCATCTGACC ACCAGCGAAA TGGATTTTTG	3600
CTGCGAGGGG CGGCGCAGGG TCGGGTAGGG CGTAGACTGG TGGTCGCTTT ACCTAAAAAC	3600
CATCGAGCTG GGTAATAAGC GTTGGCAATT TAACCGCCAG TCAGGCTTTC TTTCACAGAT	3660
GTAGCTCGAC CCATTATTG CAACCGTTAA ATTGGCGGTC AGTCCGAAAG AAAGTGCTA	3660
GTGGATTGGC GATAAAAAAC AACTGCTGAC GCCGCTGCGC GATCAGTTCA CCCGTGCACC	3720
CACCTAACCG CTATTTTTTG TTGACGACTG CGGCGACGCG CTAGTCAAGT GGGCACGTGG	3720
GCTGGATAAC GACATTGGCG TAAGTGAAGC GACCCGCATT GACCCTAACG CCTGGGTCGA	3780
CGACCTATTG CTGTAACCGC ATTCACTTCG CTGGGCGTAA CTGGGATTGC GGACCCAGCT	3780
ACGCTGGAAG GCGGCGGGCC ATTACCAGGC CGAAGCAGCG TTGTTGCAGT GCACGGCAGA	3840
TGCGACCTTC CGCCGCCCGG TAATGGTCCG GCTTCGTCGC AACACGTCA CGTGCCGTCT	3840
TACACTTGCT GATGCGGTGC TGATTACGAC CGCTCACGCG TGGCAGCATC AGGGGAAAAC	3900
ATGTGAACGA CTACGCCACG ACTAATGCTG GCGAGTGCGC ACCGTCGTAG TCCCCTTTTG	3900

FIG. 11B-5

## pICAST ALN

CTTATTTATC AGCCGGA AAA CCTACCGGAT TGATGGTAGT GGTCAAATGG CGATTACCGT	3960
GAATAAATAG TCGGCCTTTT GGATGGCCTA ACTACCATCA CCAGTTTACC GCTAATGGCA	3960
TGATGTTGAA GTGGCGAGCG ATACACCGCA TCCGGCGCGG ATTGGCCTGA ACTGCCAGCT	4020
ACTACAATT CACCGCTCGC TATGTGGCGT AGGCCGCGCC TAACCGGACT TGACGGTCGA	4020
GGCGCAGGTA GCAGAGCGGG TAACTGGCT CGGATTAGGG CCGCAAGAAA ACTATCCCGA	4080
CCGCGTCCAT CGTCTCGCCC ATTTGACCGA GCCTAATCCC GCGTTCTTT TGATAGGGCT	4080
CCGCCTTACT GCCGCCTGTT TTGACCGCTG GGATCTGCCA TTGTCAGACA TGTATACCCC	4140
GGCGGAATGA CGGCGGACAA AACTGGCGAC CCTAGACGGT AACAGTCTGT ACATATGGGG	4140
GTACGTCTTC CCGAGCGAAA ACGGTCTGCG CTGCGGGACG CGCGAATTGA ATTATGGCCC	4200
CATGCAGAAG GGCTCGCTTT TGCCAGACGC GACGCCCTGC GCGCTTAACT TAATACCGGG	4200
ACACCAGTGG CGCGGCGACT TCCAGTTCAA CATCAGCCGC TACAGTCAAC AGCAACTGAT	4260
TGTGGTCACC GCGCCGCTGA AGGTCAAGTT GTAGTCGGCG ATGTCAGTTG TCGTTGACTA	4260
GGAAACCAGC CATCGCCATC TGCTGCACGC GGAAGAAGGC ACATGGCTGA ATATCGACGG	4320
CCTTTGGTCG GTAGCGGTAG ACGACGTGCG CTTTCTTCCG TGTACCGACT TATAGCTGCC	4320
TTTCCATATG GGGATTGGTG GCGACGACTC CTGGAGCCCG TCAGTATCGG CGGAATTCCA	4380
AAAGGTATAC CCCTAACCAC CGCTGCTGAG GACCTCGGGC AGTCATAGCC GCCTTAAGGT	4380
GCTGAGCGCC GGTCGCTACC ATTACCAGTT GGTCTGGTGT CAAAAAGAT CTGGAGGTGG	4440
CGACTCGCGG CCAGCGATGG TAATGGTCAA CCAGACCACA GTTTTTTCTA GACCTCCACC	4440
TGGCAGCAGG CTTTGGCGCG CCGGATCCTT AATTAACAAT TGACCGGTAA TAATAGGTAG	4500
ACCGTCGTCC GGAACCGCGC GGCCTAGGAA TTAATTGTGA ACTGGCCATT ATTATCCATC	4500
ATAAGTGA CTGATTAGATGC ATTGATCCCT CGACCAATTC CGGTTATTTT CCACCATATT	4560
TATTCATGA CTAATCTACG TAACTAGGGA GCTGGTTAAG GCCAATAAAA GGTGGTATAA	4560
GCCGTCTTTT GGCAATGTGA GGGCCCGGAA ACCTGGCCCT GTCTTCTTGA CGAGCATTCC	4620
CGGCAGAAAA CCGTTACACT CCCGGGCCTT TGGACCGGGA CAGAAGAACT GCTCGTAAGG	4620
TAGGGGTCTT TCCCCTCTCG CCAAAGGAAT GCAAGGTCTG TTGAATGTCG TGAAGGAAGC	4680
ATCCCAGAA AGGGGAGAGC GGTTTCCTTA CGTTCAGAC AACTTACAGC ACTTCCTTCG	4680

FIG. 11B-6

## pICAST ALN

AGTTCCTCTG GAAGCTTCTT GAAGACAAAC AACGTCTGTA GCGACCCCTT GCAGGCAGCG	4740
TCAAGGAGAC CTTTGAAGAA CTTCTGTTTG TTGCAGACAT CGCTGGGAAA CGTCCGTCGC	4740
GAACCCCCCA CCTGGCGACA GGTGCCTCTG CGGCCAAAAG CCACGTGTAT AAGATACACC	4800
CTTGGGGGGT GGACCGCTGT CCACGGAGAC GCCGGTTTC GGTGCACATA TTCTATGTGG	4800
TGCAAAGGCG GCACAACCCC AGTGCCACGT TGTGAGTTGG ATAGTTGTGG AAAGAGTCAA	4860
ACGTTTCCGC CGTGTGGGG TCACGGTGCA AACTCAACC TATCAACACC TTTCTCAGTT	4860
ATGGCTCTCC TCAAGCGTAT TCAACAAGGG GCTGAAGGAT GCCCAGAAGG TACCCATTG	4920
TACCGAGAGG AGTTCGCATA AGTTGTTCCC GACTTCTTA CGGTCTTCC ATGGGGTAAC	4920
TATGGGATCT GATCTGGGGC CTCGGTGAC ATGCTTTACA TGTGTTTAGT CGAGGTAA	4980
ATACCTAGA CTAGACCCCG GAGCCACGTG TACGAAATGT ACACAAATCA GCTCCAATTT	4980
AAACGTCTAG GCCCCCGAA CCACGGGGAC GTGGTTTTCC TTTGAAAAAC ACGATGATAA	5040
TTTGAGATC CGGGGGGCTT GGTGCCCTG CACCAAAGG AACTTTTTG TGCTACTATT	5040
TACCATGATT GAACAAGATG GATTGCACGC AGGTTCTCCG GCCGCTTGGG TGGAGAGGCT	5100
ATGGTACTAA CTTGTTCTAC CTAACGTGCG TCCAAGAGGC CGGCGAACCC ACCTCTCCGA	5100
ATTCGGCTAT GACTGGGCAC AACAGACAAT CGGCTGCTCT GATGCCGCCG TGTTCGGCT	5160
TAAGCCGATA CTGACCCGTG TTGTCTGTTA GCCGACGAGA CTACGGCGGC ACAAGGCCGA	5160
GTCAGCGCAG GGGCGCCCGG TTCTTTTTGT CAAGACCGAC CTGTCCGGTG CCCTGAATGA	5220
CAGTCGCGTC CCCGCGGGCC AAGAAAAACA GTTCTGGCTG GACAGGCCAC GGGACTTACT	5220
ACTGCAGGAC GAGGCAGCGC GGCTATCGTG GCTGGCCACG ACGGGCGTTC CTTGCGCAGC	5280
TGACGTCCTG CTCCGTGCGC CCGATAGCAC CGACCGGTGC TGCCCGCAAG GAACGCGTCG	5280
TGTGCTCGAC GTTGTCACTG AAGCGGGAAG GGAAGGCTG CTATTGGGCG AAGTGCCGGG	5340
ACACGAGCTG CAACAGTGAC TTCGCCCTTC CCTGACCGAC GATAACCCGC TTCACGGCCC	5340
GCAGGATCTC CTGTCATCTC ACCTTGCTCC TGCCGAGAAA GTATCCATCA TGGCTGATGC	5400
CGTCCTAGAG GACAGTAGAG TGGAACGAGG ACGGCTCTTT CATAGGTAGT ACCGACTACG	5400
AATGCGGCGG CTGCATACGC TTGATCCGGC TACCTGCCCA TTCGACCACC AAGCGAAACA	5460
TTACGCCGCC GACGTATGCG AACTAGGCCG ATGGACGGT AAGCTGGTGG TTCGCTTTGT	5460

FIG. 11B-7

## pICAST ALN

TCGCATCGAG CGAGCACGTA CTCGG/ATGGA AGCCGGTCTT GTCGATCAGG ATGATCTGGA	5520
AGCGTAGCTC GCTCGTGCAT GAGCCTACCT TCGGCCAGAA CAGCTAGTCC TACTAGACCT	5520
CGAAGAGCAT CAGGGGCTCG CGCCAGCCGA ACTGTTCGCC AGGCTCAAGG CGCGCATGCC	5580
GCTTCTCGTA GTCCCCGAGC GCGGTCTGGCT TGACAAGCGG TCCGAGTTCC GCGCGTACGG	5580
CGACGGCGAG GATCTCGTCG TGACCCATGG CGATGCCTGC TTGCCGAATA TCATGGTGGA	5640
GCTGCCGCTC CTAGAGCAGC ACTGGGTACC GCTACGGACG AACGGCTTAT AGTACCACCT	5640
AAATGGCCGC TTTTCTGGAT TCATCGACTG TGGCCGGCTG GGTGTGGCGG ACCGCTATCA	5700
TTTACCGCG AAAAGACCTA AGTAGCTGAC ACCGGCCGAC CCACACCGCC TGGCGATAGT	5700
GGACATAGCG TTGGCTACCC GTGATATTGC TGAAGAGCTT GGC GGCGAAT GGGCTGACCG	5760
CCTGTATCGC AACCGATGGG CACTATAACG ACTTCTCGAA CCGCCGCTTA CCCGACTGGC	5760
CTTCCTCGTG CTTTACGGTA TCGCCGCTCC CGATTGCGAG CGCATCGCCT TCTATCGCCT	5820
GAAGGAGCAC GAAATGCCAT AGCGGCGAGG GCTAAGCGTC GCGTAGCGGA AGATAGCGGA	5820
TCTTGACGAG TTCTTCTGAG CGGGACTCTG GGGTTCGCAT CGATAAAATA AAAGATTTTA	5880
AGAACTGCTC AAGAAGACTC GCCCTGAGAC CCAAGCGTA GCTATTTTAT TTTCTAAAT	5880
TTTAGTCTCC AGAAAAAGGG GGAATGAAA GACCCACCT GTAGGTTTGG CAAGCTAGCT	5940
AAATCAGAGG TCTTTTCCC CCCTTACTTT CTGGGGTGA CATCCAAACC GTTCGATCGA	5940
TAAGTAACGC CATTTTGCAA GGCATGGAAA AATACATAAC TGAGAATAGA GAAGTTCAGA	6000
ATTCATTGCG GTAAAACGTT CCGTACCTTT TTATGTATTG ACTCTTATCT CTTCAAGTCT	6000
TCAAGGTCAG GAACAGATGG AACAGCTGAA TATGGGCCAA ACAGGATATC TGTGGTAAGC	6060
AGTTCCAGTC CTTGTCTACC TTGTGACTT ATACCCGGTT TGTCCTATAG ACACCATTG	6060
AGTTCCTGCC CCGGCTCAGG GCCAAGAACA GATGGAACAG CTGAATATGG GCCAAACAGG	6120
TCAAGGACGG GGCCGAGTCC CGGTTCTTGT CTACCTTGTC GACTTATACC CGGTTTGTCC	6120
ATATCTGTGG TAAGCAGTTC CTGCCCCGGC TCAGGGCCAA GAACAGATGG TCCCAGATG	6180
TATAGACACC ATTCGTCAAG GACGGGGCCG AGTCCCGGTT CTTGTCTACC AGGGGTCTAC	6180
CGGTCCAGCC CTCAGCAGTT TCTAGAGAAC CATCAGATGT TTCCAGGGTG CCCAAGGAC	6240
GCCAGGTCGG GAGTCGTCAA AGATCTCTTG GTAGTCTACA AAGGTCCAC GGGGTTCTG	6240

FIG. 11B-8

## pICAST ALN

CTGAAATGAC CCTGTGCCTT ATTTGAACTA ACCAATCAGT TCGCTTCTCG CTTCTGTTTCG	6300
GACTTTACTG GGACACGGAA TAACTTGAT TGGTTAGTCA AGCGAAGAGC GAAGACAAGC	6300
CGCGCTTCTG CTCCCCGAGC TCAATAAAAG AGCCCACAAC CCCTCACTCG GGGCGCCAGT	6360
GCGCGAAGAC GAGGGGCTCG AGTTATTTTC TCGGGTGTG GGGAGTGAGC CCCGCGGTCA	6360
CCTCCGATTG ACTGAGTCGC CCGGGTACCC GTGTATCCAA TAAACCCTCT TGCAGTTGCA	6420
GGAGGCTAAC TGACTCAGCG GGCCCATGGG CACATAGGTT ATTTGGGAGA ACGTCAACGT	6420
TCCGACTTGT GGTCTCGCTG TTCCTTGGGA GGGTCTCCTC TGAGTGATTG ACTACCCGTC	6480
AGGCTGAACA CCAGAGCGAC AAGGAACCCT CCCAGAGGAG ACTCACTAAC TGATGGGCAG	6480
AGCGGGGGTC TTTCATTCAT GCAGCATGTA TCAAAATTAA TTTGGTTTTT TTTCTTAAGT	6540
TCGCCCCCAG AAAGTAAGTA CGTCGTACAT AGTTTTAATT AAACCAAAAA AAAGAATTCA	6540
ATTTACATTA AATGGCCATA GTTGCAATTA TGAATCGGCC AACGCGCGGG GAGAGGCGGT	6600
TAAATGTAAT TTACCGGTAT CAACGTAATT ACTTAGCCGG TTGCGCGCCC CTCTCCGCCA	6600
AACGCATAAC CGCGAGAAGG CGAAGGAGCG AGTGACTGAG CGACGCGAGC CAGCAAGCCG	6660
TTGCGTATTG GCGCTCTTCC GCTTCCTCGC TCACTGACTC GCTGCGCTCG GTCGTTCCGC	6660
TGCGGCGAGC GGTATCAGCT CACTCAAAGG CGGTAATACG GTTATCCACA GAATCAGGGG	6720
ACGCCGCTCG CCATAGTCGA GTGAGTTTCC GCCATTATGC CAATAGGTGT CTTAGTCCCC	6720
ATAACGCAGG AAAGAACATG TGAGCAAAAG GCCAGCAAAA GGCCAGGAAC CGTAAAAAGG	6780
TATTGCGTCC TTTCTTGTAC ACTCGTTTTT CGGTCGTTTT CCGGTCCTTG GCATTTTTTC	6780
CCGCGTTGCT GGCCTTTTTT CATAGGCTCC GCCCCCTGA CGAGCATCAC AAAAATCGAC	6840
GGCGCAACGA CCGCAAAAAG GTATCCGAGG CGGGGGGACT GCTCGTAGTG TTTTLAGCTG	6840
GCTCAAGTCA GAGGTGGCGA AACCCGACAG GACTATAAAG ATACCAGGCG TTTCCCCCTG	6900
CGAGTTCAGT CTCCACCGCT TTGGGCTGTC CTGATATTTT TATGGTCCGC AAAGGGGGAC	6900
GAAGCTCCCT CGTGCGCTCT CCTGTTCCGA CCCTGCCGCT TACCGGATAC CTGTCCGCCT	6960
CTTCGAGGGA GCACGCGAGA GGACAAGGCT GGGACGGCGA ATGGCCTATG GACAGGCGGA	6960
TTCTCCCTTC GGGAAAGCGTG GCGCTTCTC ATAGCTCAG CTGTAGGTAT CTCAGTTCGG	7020
AAGAGGGAAG CCCTTCGCAC CGCGAAAGAG TATCGAGTGC GACATCCATA GAGTCAAGCC	7020

FIG. 11B-9

## pICAST ALN

TGTAGGTCGT TCGCTCCAAG CTGGGCTGTG TGCACGAACC CCCC GTTCAG CCCGACCGCT	7080
ACATCCAGCA AGCGAGGTTC GACCCGACAC ACGTGCTTGG GGGGCAAGTC GGGCTGGCGA	7080
GCGCCTTATC CGGTAAC TAT CGTCTTGAGT CCAACCCGGT AAGACACGAC TTATCGCCAC	7140
CGCGGAATAG GCCATTGATA GCAGAACTCA GGTG GGGCCA TTCTGTGCTG AATAGCGGTG	7140
TGGCAGCAGC CACTGGTAAC AGGATTAGCA GAGCGAGGTA TGTAGGCGGT GCTACAGAGT	7200
ACCGTCGTCG GTGACCATTG TCCTAATCGT CTCGCTCCAT ACATCCGCCA CGATGTCTCA	7200
TCTTGAAGTG GTGGCCTAAC TACGGCTACA CTAGAAGAAC AGTATTTGGT ATCTGCGCTC	7260
AGAACTTCAC CACCGGATTG ATGCCGATGT GATCTTCTTG TCATAAACCA TAGACGCGAG	7260
TGCTGAAGCC AGTTACCTTC GGAAAAAGAG TTGGTAGCTC TTGATCCGGC AAACAAACCA	7320
ACGACTTCGG TCAATGGAAG CCTTTTTCTC AACCATCGAG AACTAGGCCG TTTGTTTGGT	7320
CCGCTGGTAG CGGTGGTTTT TTTGTTTGCA AGCAGCAGAT TACGCGCAGA AAAAAAGGAT	7380
GGCGACCATC GCCACCAAAA AAACAAACGT TCGTCGTCTA ATGCGCGTCT TTTTTCTA	7380
CTCAAGAAGA TCCTTTGATC TTTTCTACGG GGTCTGACGC TCAGTGGAAC GAAAACTCAC	7440
GAGTTCTTCT AGGAAACTAG AAAAGATGCC CCAGACTGCG AGTCACCTTG CTTTTGAGTG	7440
GTTAAGGGAT TTTGGTCATG AGATTATCAA AAAGGATCTT CACCTAGATC CTTTTGCGGC	7500
CAATTCCTA AAACCACTAC TCTAATAGTT TTCTCTAGAA GTGGATCTAG GAAAACGCCG	7500
CGCAAATCAA TCTAAAGTAT ATATGAGTAA ACTTGGTCTG ACAGTTACCA ATGCTTAATC	7560
GCGTTTAGTT AGATTTTATA TATACTCATT TGAACCAGAC TGTCAATGGT TACGAATTAG	7560
AGTGAGGCAC CTATCTCAGC GATCTGTCTA TTTCGTTTAT CCATAGTTGC CTGACTCCCC	7620
TCACTCCGTG GATAGAGTCG CTAGACAGAT AAAGCAAGTA GGTATCAACG GACTGAGGGG	7620
GTCGTGTAGA TAACTACGAT ACGGGAGGGC TTACCATCTG GCCCCAGTGC TGCAATGATA	7680
CAGCACATCT ATTGATGCTA TGCCCTCCCG AATGGTAGAC CGGGGTCACG ACGTTACTAT	7680
CCGCGAGACC CACGCTCACC GGCTCCAGAT TTATCAGCAA TAAACCAGCC AGCCGGAAGG	7740
GGCGCTCTGG GTGCGAGTGG CCGAGGTCTA AATAGTCGTT ATTTGGTCGG TCGGCCTTCC	7740
GCCGAGCGCA GAAGTGGTCC TGCAACTTTA TCCGCCTCCA TCCAGTCTAT TAATTGTTGC	7800
CGGCTCGCGT CTTCAACAGG ACGTTGAAAT AGGCGGAGGT AGGTCAGATA ATTAACAACG	7800

FIG.11B-10



## pICAST ALN

CGGGAAGCTA GAGTAAGTAG TTCGCCAGTT AATAGTTTGC GCAACGTTGT TGCCATTGCT	7860
GCCCTTCGAT CTCATTATC AAGCGGTCAA TTATCAAACG CGTTGCAACA ACGGTAACGA	7860
ACAGGCATCG TGGTGTACG CTCGTCGTTT GGTATGGCTT CATTAGCTC CGGTTCCCAA	7920
TGTCCGTAGC ACCACAGTGC GAGCAGCAA CCATACCGAA GTAAGTCGAG GCCAAGGGTT	7920
CGATCAAGGC GAGTTACATG ATCCCCATG TTGTGCAAAA AAGCGGTTAG CTCCTTCGGT	7980
GCTAGTTCCG CTCAATGTAC TAGGGGGTAC AACACGTTTT TTCGCCAATC GAGGAAGCCA	7980
CCTCCGATCG TTGTCAGAAG TAAGTTGGCC GCAGTGTTAT CACTCATGGT TATGGCAGCA	8040
GGAGGCTAGC AACAGTCTT ATTCAACCGG CGTCACAATA GTGAGTACCA ATACCGTCGT	8040
CTGCATAATT CTCTTACTGT CATGCCATCC GTAAGATGCT TTTCTGTGAC TGGTGAGTAC	8100
GACGTATTAA GAGAATGACA GTACGGTAGG CATTCTACGA AAAGACACTG ACCACTCATG	8100
TCAACCAAGT CATTCTGAGA ATAGTGTATG CGGCGACCGA GTTGCTCTTG CCCGGCGTCA	8160
AGTTGGTTCA GTAAGACTCT TATCACATAC GCCGCTGGCT CAACGAGAAC GGGCCGCAGT	8160
ATACGGGATA ATACCGCGCC ACATAGCAGA ACTTTAAAAG TGCTCATCAT TGGAAAACGT	8220
TATGCCCTAT TATGGCGCGG TGTATCGTCT TGAAATTTTC ACGAGTAGTA ACCTTTTGCA	8220
TCTTCGGGGC GAAAACTCTC AAGGATCTTA CCGCTGTTGA GATCCAGTTC GATGTAACCC	8280
AGAAGCCCCG CTTTTGAGAG TTCCTAGAAT GGCAGAACT CTAGGTCAAG CTACATTGGG	8280
ACTCGTGCAC CCAACTGATC TTCAGCATCT TTTACTTTCA CCAGCGTTTC TGGGTGAGCA	8340
TGAGCACGTG GGTGACTAG AAGTCGTAGA AAATGAAAGT GGTCGCAAAG ACCCACTCGT	8340
AAACAGGAA GGCAAAATGC CGCAAAAAG GGAATAAGGG CGACACGGAA ATGTTGAATA	8400
TTTTGTCCTT CCGTTTTACG GCGTTTTTC CTTATTCCC GCTGTGCCTT TACAACTTAT	8400
CTCATACTCT TCCTTTTTCA ATATTATTGA AGCATTATC AGGGTTATTG TCTCATGAGC	8460
GAGTATGAGA AGGAAAAAGT TATAATACT TCGTAAATAG TCCAATAAC AGAGTACTCG	8460
GGATACATAT TTGAATGTAT TTAGAAAAAT AACAAATAG GGGTTCCGCG CACATTTT	8518
CCTATGTATA AACTTACATA AATCTTTTTA TTGTTTATC CCAAGGCGC GTGTAAAG	8518

FIG.11B-11

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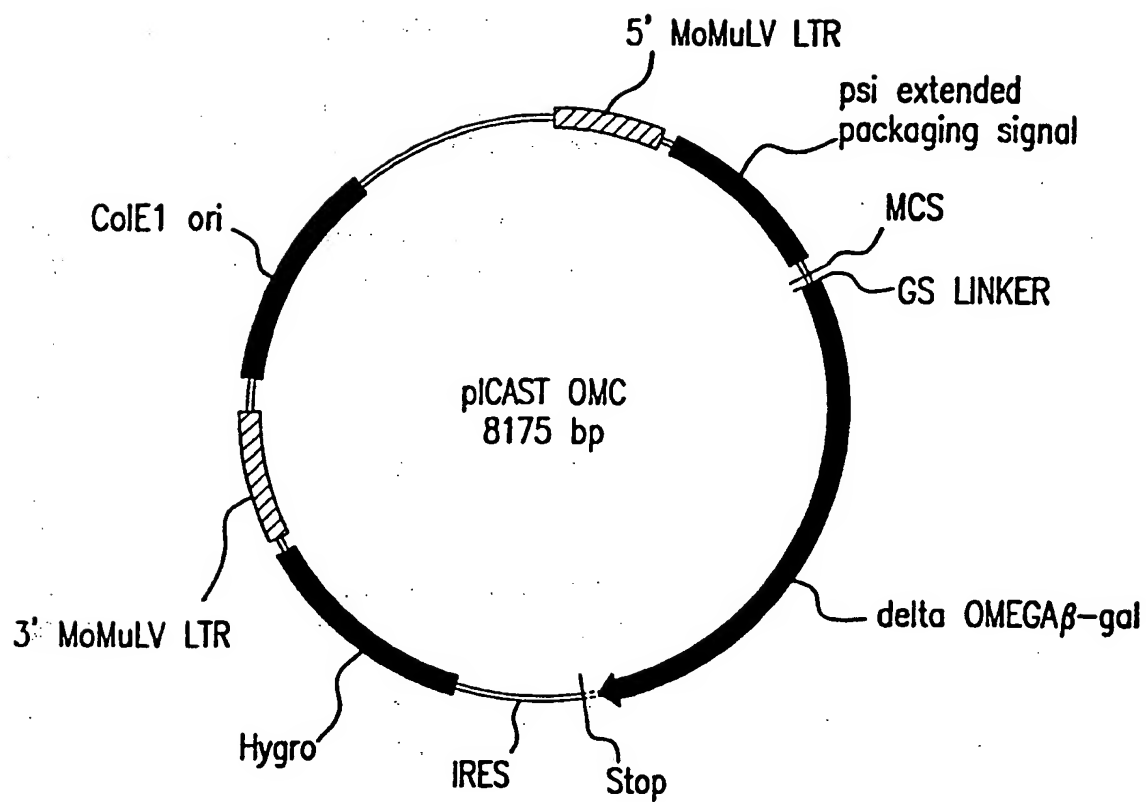


FIG.12A

## pICAST OMC

CTGCAGCCTG AATATGGGCC AACAGGATA TCTGTGGTAA GCAGTTCCTG CCCC GGCTCA	60
GACGTCGGAC TTATACCCGG TTTGTCCTAT AGACACCATT CGTCAAGGAC GGGGCCGAGT	60
GGGCCAAGAA CAGATGGAAC AGCTGAATAT GGGCCAAACA GGATATCTGT GGTAAGCAGT	120
CCCGGTTCTT GTCTACCTTG TCGACTTATA CCCGGTTTGT CCTATAGACA CCATTCGTCA	120
TCCTGCCCCG GCTCAGGGCC AAGAACAGAT GGTCCCCAGA TGCGGTCCAG CCCTCAGCAG	180
AGGACGGGGC CGAGTCCCGG TTCTTGCTTA CCAGGGGTCT ACGCCAGGTC GGGAGTCGTC	180
TTTCTAGAGA ACCATCAGAT GTTTCAGGG TGCCCCAAGG ACCTGAAATG ACCCTGTGCC	240
AAAGATCTCT TGGTAGTCTA CAAAGGTCCC ACGGGGTTCC TGGACTTTAC TGGGACACGG	240
TTATTTGAAC TAACCAATCA GTTCGCTTCT CGCTTCTGTT CGCGCGCTTC TGCTCCCCGA	300
AATAAACTTG ATTGGTTAGT CAAGCGAAGA GCGAAGACAA GCGCGCGAAG ACGAGGGGCT	300
GCTCAATAAA AGAGCCCAACA ACCCTCACT CGGGGCGCCA GTCCTCCGAT TGA CTGAGTC	360
CGAGTTATTT TCTCGGGTGT TGGGGAGTGA GCCCGCGGT CAGGAGGCTA ACTGACTCAG	360
GCCCGGGTAC CCGTGTATCC AATAAACCTT CTTGCAGTTG CATCCGACTT GTGGTCTCGC	420
CGGGCCCATG GGCACATAGG TTATTTGGGA GAACGTCAAC GTAGGCTGAA CACCAGAGCG	420
TGTTCTTGG GAGGYTCTCC TCTGAGTGAT TGA CTACCCG TCAGCGGGGG TCTTTCATTT	480
ACAAGGAACC CTCCAGAGG AGACTCACTA ACTGATGGGC AGTCGCCCCC AGAAAGTAA	480
GGGGGCTCGT CCGGGATCGG GAGACCCCTG CCCAGGGACC ACCGACCCAC CACCGGGAGG	540
CCCCGAGCA GGCCCTAGCC CTCTGGGGAC GGGTCCCTGG TGGCTGGGTG GTGGCCCTCC	540
CAAGCTGGCC AGCAACTTAT CTGTGTCTGT CCGATTGTCT AGTGTCTATG ACTGATTTTA	600
GTTCGACCGG TCGTTGAATA GACACAGACA GGCTAACAGA TCACAGATAC TGA CTAAAAT	600
TGCGCCTGCG TCGGTACTAG TTAGCTAACT AGCTCTGTAT CTGGCGGACC CGTGGTGGAA	660
ACGCGGACGC AGCCATGATC AATCGATTGA TCGAGACATA GACCGCCTGG GCACCACCTT	660
CTGACGAGTT CTGAACACCC GGCCGCAACC CTGGGAGACG TCCAGGGAC TTTGGGGGCC	720
GACTGTCAA GACTTGTTGG CCGGCGTTGG GACCCTCTGC AGGGTCCCTG AAACCCCGG	720
GTTTTTGTGG CCCGACCTGA GGAAGGGAGT CGATGTGGAA TCCGACCCCG TCAGGATATG	780
CAAAAACACC GGGCTGGACT CCTTCCCTCA GCTACACCTT AGGCTGGGGC AGTCCTATAC	780

FIG.12B-1

## pICAST OMC

TGGTTCTGGT AGGAGACGAG AACCTAAAAC AGTTCCCGCC TCCGTCTGAA TTTTGTCTTT	840
ACCAAGACCA TCCTCTGCTC TTGGATTTTG TCAAGGGCGG AGGCAGACTT AAAAACGAAA	840
CGGTTTGGA CCGAAGCCGC GCGTCTTGTC TGCTGCAGCA TCGTTCTGTG TTGTCTCTGT	900
GCCAAACCTT GGCTTCGGCG CGCAGAACAG ACGACGTCGT AGCAAGACAC AACAGAGACA	900
CTGACTGTGT TTCTGTATTT GTCTGAAAAT TAGGGCCAGA CTGTTACCAC TCCCTTAAGT	960
GACTGACACA AAGACATAAA CAGACTTTTA ATCCCGGTCT GACAATGGTG AGGGAATTCA	960
TTGACCTTAG GTAACCTGGA AGATGTGCGAG CGGCTCGCTC ACAACCAGTC GGTAGATGTC	1020
AACTGGAATC CATTGACCTT TCTACAGCTC GCCGAGCGAG TGTTGGTCAG CCATCTACAG	1020
AAGAAGAGAC GTTGGGTTAC CTTCTGCTCT GCAGAATGGC CAACCTTTAA CGTCGGATGG	1080
TTCTTCTCTG CAACCCAATG GAAGACGAGA CGTCTTACCG GTTGGAATT GCAGCCTACC	1080
CCGCGAGACG GCACCTTTAA CCGAGACCTC ATCACCAGG TTAAGATCAA GGTCTTTTCA	1140
GGCGCTCTGC CGTGGAAATT GGCTCTGGAG TAGTGGGTCC AATTCTAGTT CCAGAAAAGT	1140
CCTGGCCCGC ATGGACACCC AGACCAGGTC CCCTACATCG TGACCTGGGA AGCCTTGGCT	1200
GGACCGGGCG TACCTGTGGG TCTGGTCCAG GGGATGTAGC ACTGGACCCT TCGGAACCGA	1200
TTTGACCCCC CTCCTGGGT CAAGCCCTTT GTACACCCTA AGCCTCCGCC TCCTCTTCTT	1260
AACTGGGGG GAGGGACCCA GTTCGGGAAA CATGTGGGAT TCGGAGGCGG AGGAGAAGGA	1260
CCATCCGCCC CGTCTCTCCC CTTGAACCT CCTCGTTCGA CCGCGCTCG ATCCTCCCTT	1320
GGTAGGCGGG GCAGAGAGGG GGAACCTGGA GGAGCAAGCT GGGGCGGAGC TAGGAGGGAA	1320
TATCCAGCCC TCACTCCTTC TCTAGGCGCC GGCCGCTCTA GCCCATTAAT ACGACTCACT	1380
ATAGGTCGGG AGTGAGGAAG AGATCCGCGG CCGGCGAGAT CGGGTAATTA TGCTGAGTGA	1380
ATAGGGCGAT TCGAATCAGG CTTGGCGCG CCGGATCCTT AATTAAGCGC AATTGGGAGG	1440
TATCCGCTA AGCTTAGTCC GGAACCGCG GGCCTAGGAA TTAATTCGCG TTAACCCTCC	1440
TGGCGGTAGC CTCGAGATGG GCGTGATTAC GGATTCAGTG GCCGTCGTTT TACAACGTCG	1500
ACCGCCATCG GAGCTCTACC CGCACTAATG CTAAGTGAC CGGCAGCAA ATGTTGCAGC	1500
TGACTGGGAA AACCCTGGCG TTACCCAAT TAATCGCCTT GCAGCACATC CCCCTTTCGC	1560
ACTGACCCTT TTGGGACCGC AATGGGTTGA ATTAGCGGAA CGTCGTGTAG GGGGAAAGCG	1560

FIG. 12B-2

## pICAST OMC

CAGCTGGCGT AATAGCGAAG AGGCCCCGAC CGATCGCCCT TCCCAACAGT TACGCAGCCT	1620
GTGACCGCA TTATCGCTTC TCCGGGCGTG GCTAGCGGGA AGGGTTGTCA ATGCGTCGGA	1620
GAATGGCGAA TGGCGCTTTG CCTGGTTTCC GGCACCAGAA GCGGTGCCGG AAAGCTGGCT	1680
CTTACCGCTT ACCGCGAAAC GGACCAAAGG CCGTGGTCTT CGCCACGGCC TTTCGACCGA	1680
GGAGTGCGAT CTTCTGAGG CCGATACTGT CGTCGTCCCC TCAAAGTGGC AGATGCACGG	1740
CCTCACGCTA GAAGGACTCC GGCTATGACA GCAGCAGGGG AGTTTGACCG TCTACGTGCC	1740
TTACGATGCG CCCATCTACA CCAACGTGAC CTATCCCATT ACGGTCAATC CGCCGTTTGT	1800
AATGCTACGC GGGTAGATGT GGTGCACTG GATAGGGTAA TGCCAGTTAG GCGGCAACA	1800
TCCCACGGAG AATCCGACGG GTTGTTACTC GCTCACATTT AATGTTGATG AAAGCTGGCT	1860
AGGGTGCCCTC TTAGGCTGCC CAACAATGAG CGAGTGTAAG TTACAACCTAC TTTCGACCGA	1860
ACAGGAAGGC CAGACGCGAA TTATTTTTGA TGGCGTTAAC TCGGCGTTTC ATCTGTGGTG	1920
TGTCCTTCCG GTCTGCGCTT AATAAAACT ACCGCAATTG AGCCGCAAAG TAGACACCAC	1920
CAACGGGCGC TGGGTGCGTT ACGGCCAGGA CAGTCGTTTG CCGTCTGAAT TTGACCTGAG	1980
GTTGCCCGCG ACCCAGCCAA TGCCGGTCCT GTCAGCAAAC GGCAGACTTA AACTGGACTC	1980
CGCATTTTTA CGCGCCGGAG AAAACCGCCT CGCGGTGATG GTGCTGCGCT GGAGTGACGG	2040
GCGTAAAAAT GCGCGGCCTC TTTTGGCGGA GCGCCACTAC CACGACGCGA CCTACTGCC	2040
CAGTTATCTG GAAGATCAGG ATATGTGGCG GATGAGCGGC ATTTTCCGTG ACGTCTCGTT	2100
GTCAATAGAC CTTCTAGTCC TATACACCGC CTAATCGCCG TAAAAGGCAC TGCAGAGCAA	2100
GCTGCATAAA CCGACTACAC AAATCAGCGA TTTCCATGTT GCCACTCGCT TTAATGATGA	2160
CGACGTATTT GGCTGATGTG TTTAGTCGCT AAAGGTACAA CCGTGAGCGA AATTACTACT	2160
TTTCAGCCGC GCTGTACTGG AGGCTGAAGT TCAGATGTGC GGCAGATTGC GTGACTACCT	2220
AAAGTCGGCG CGACATGACC TCCGACTTCA AGTCTACACG CCGCTCAACG CACTGATGGA	2220
ACGGGTAACA GTTTCTTTAT GGCAGGGTGA AACGCAGGTC GCCAGCGGCA CCGCGCCTTT	2280
TGCCATTGT CAAAGAAATA CCGTCCCACT TTGCGTCCAG CCGTCGCCGT GGCAGGAAA	2280
CGGCGGTGAA ATTATCGATG AGCGTGGTGG TTATGCCGAT CGCGTCACAC TACGTCTGAA	2340
GCCGCCACTT TAATAGCTAC TCGCACCACC AATACGGCTA GCGCAGTGTG ATGCAGACTT	2340

FIG. 12B-3

## pICAST OMC

CGTCGAAAAC CCGAAACTGT GGAGCGCCGA AATCCCGAAT CTCTATCGTG CGGTGGTTGA	2400
GCAGCTTTTG GGCTTTGACA CCTCGCGGCT TTAGGGCTTA GAGATAGCAC GCCACCAACT	2400
ACTGCACACC GCCGACGGCA CGCTGATTGA AGCAGAAGCC TGCATGTGCG GTTTCGCGA	2460
TGACGTGTGG CGGCTGCCGT GCGACTAAT TCCTCTTCGG ACGCTACAGC CAAAGGCGCT	2460
GGTGCGGATT GAAAATGGTC TGCTGCTGCT GAACGGCAAG CCGTTGCTGA TTCGAGGCGT	2520
CCACGCCTAA CTTTACCAG ACGACGACGA CTTGCCGTTT GGCAACGACT AAGCTCCGCA	2520
TAACCGTCAC GAGCATCATC CTCTGCATGG TCAGGTCATG GATGAGCAGA CGATGGTGCA	2580
ATTGGCAGTG CTCGTAGTAG GAGACGTACC AGTCCAGTAC CTACTCGTCT GCTACCACGT	2580
GGATATCCTG CTGATGAAGC AGAACAATT TAACGCCGTG CGCTGTTTCG ATTATCCGAA	2640
CCTATAGGAC GACTACTTCG TCTTGTTGAA ATTGCGGCAC GCGACAAGCG TAATAGGCTT	2640
CCATCCGCTG TGGTACACGC TGTGCGACCG CTACGGCCTG TATGTGGTGG ATGAAGCCAA	2700
GGTAGGCGAC ACCATGTGCG ACACGCTGGC GATGCCGGAC ATACACCACC TACTTCGGTT	2700
TATTGAAACC CACGGCATGG TGCCAATGAA TCGTCTGACC GATGATCCGC GCTGGCTACC	2760
ATAACTTTGG GTGCCGTACC ACGGTTACTT AGCAGACTGG CTACTAGGCG CGACCGATGG	2760
GGCGATGAGC GAACGCGTAA CGCGAATGGT GCAGCGCGAT CGTAATCACC CGAGTGTGAT	2820
CCGCTACTCG CTTGCGCATT GCGCTTACCA CGTCGCGCTA GCATTAGTGG GCTCACACTA	2820
CATCTGGTCG CTGGGGAATG AATCAGGCCA CGGCGCTAAT CACGACGCGC TGTATCGCTG	2880
GTAGACCAGC GACCCCTTAC TTAGTCCGGT GCCGCGATTA GTGCTGCGCG ACATAGCGAC	2880
GATCAAATCT GTCGATCCTT CCCGCCCGGT GCAGTATGAA GGCGGCGGAG CCGACACCAC	2940
CTAGTTTAGA CAGCTAGGAA GGGCGGGCCA CGTCATACTT CCGCCGCCTC GGCTGTGGTG	2940
GGCCACCGAT ATTATTTGCC CGATGTACGC GCGCGTGGAT GAAGACCAGC CCTTCCCGGC	3000
CCGGTGGCTA TAATAAACGG GCTACATGCG CGCGCACCTA CTTCTGGTCG GGAAGGGCCG	3000
TGTGCCGAAA TGGTCCATCA AAAAATGGCT TTCGCTACCT GGAGAGACGC GCCCGCTGAT	3060
ACACGGCTTT ACCAGGTAGT TTTTACCGA AAGCGATGGA CCTCTCTGCG CGGGCGACTA	3060
CCTTTGCGAA TACGCCCACG CGATGGGTAA CAGTCTTGGC GGTTCGCTA AATACTGGCA	3120
GGAAACGCTT ATGCGGGTGC GCTACCCATT GTCAGAACCG CCAAAGCGAT TTATGACCGT	3120

FIG. 12B-4

## pICAST OMC

GGCGTTTCGT CAGTATCCCC GTTTACAGGG CGGCTTCGTC TGGGACTGGG TGGATCAGTC 3180  
CCGCAAAGCA GTCATAGGGG CAAATGTCCC GCCGAAGCAG ACCCTGACCC ACCTAGTCAG 3180  
  
GCTGATTAAG TATGATGAAA ACGGCAACCC GTGGTCGGCT TACGGCGGTG ATTTTGGCGA 3240  
CGACTAATTT ATACTACTTT TGCCGTTGGG CACCAGCCGA ATGCCGCCAC TAAAACCGCT 3240  
  
TACGCCGAAC GATCGCCAGT TCTGTATGAA CGGTCTGGTC TTTGCCGACC GCACGCCGCA 3300  
ATGCGGCTTG CTAGCGGTCA AGACATACTT GCCAGACCAG AAACGGCTGG CGTGCGGGCT 3300  
  
TCCAGCGCTG ACGGAAGCAA AACACCAGCA GCAGTTTTTC CAGTTCCGTT TATCCGGGCA 3360  
AGGTGCGGAC TGCCTTCGTT TTGTGGTCGT CGTCAAAAAG GTCAGGCAA ATAGGCCCGT 3360  
  
AACCATCGAA GTGACCAGCG AATACCTGTT CCGTCATAGC GATAACGAGC TCCTGCACTG 3420  
TTGGTAGCTT CACTGGTCGC TTATGGACAA GGCAGTATCG CTATTGCTCG AGGACGTGAC 3420  
  
GATGGTGGCG CTGGATGGTA AGCCGCTGGC AAGCGGTGAA GTGCCTCTGG ATGTCGCTCC 3480  
CTACCACCGC GACCTACCAT TCGGCGACCG TTCGCCACTT CACGGAGACC TACAGCGAGG 3480  
  
ACAAGGTAAA CAGTTGATTG AACTGCCTGA ACTACCGCAG CCGGAGAGCG CCGGGCAACT 3540  
TGTTCCATTT GTCAACTAAC TTGACGGACT TGATGGCGTC GGCCTCTCGC GGCCCGTTGA 3540  
  
CTGGCTCACA GTACGCGTAG TGCAACCGAA CGCGACCGCA TGGTCAGAAG CCGGGCACAT 3600  
GACCGAGTGT CATGCGCATC ACGTTGGCTT GCGCTGGCGT ACCAGTCTTC GGCCCGTGTA 3600  
  
CAGCGCCTGG CAGCAGTGGC GTCTGGCGGA AAACCTCAGT GTGACGCTCC CCGCCGCGTC 3660  
GTCGCGGACC GTCGTCACCG CAGACCGCCT TTTGGAGTCA CACTGCGAGG GGCGGCGCAG 3660  
  
CCACGCCATC CCGCATCTGA CCACCAGCGA AATGGATTTT TGCATCGAGC TGGGTAATAA 3720  
GGTGCGGTAG GGCCTAGACT GGTGGTCGCT TTACCTAAAA ACGTAGCTCG ACCCATTATT 3720  
  
GCGTTGGCAA TTTAACCGCC AGTCAGGCTT TCTTTCACAG ATGTGGATTG GCGATAAAAA 3780  
CGCAACCGTT AAATTGGCGG TCAGTCCGAA AGAAAGTGTC TACACCTAAC CGCTATTTTT 3780  
  
ACAAGTCTG ACGCCGCTGC GCGATCAGTT CACCCGTGTC GATAGATCTG AACAGAACT 3840  
TGTTGACGAC TCGGGCGACG CGTAGTCAA GTGGGCACAG CTATCTAGAC TTGTCTTTGA 3840  
  
CATTTCCGAA GAAGACCTAG TCGACCATCA TCATCATCAT CACCGGTAAT AATAGGTAGA 3900  
GTAAAGGCTT CTTCTGGATC AGCTGGTAGT AGTAGTAGTA GTGGCCATTA TTATCCATCT 3900

FIG.12B-5

## pICAST OMC

TAAGTGACTG ATTAGATGCA TTTCGACTAG ATCCCTCGAC CAATTCCGGT TATTTTCCAC	3960
ATTCAGTGAC TAATCTACGT AAAGCTGATC TAGGGAGCTG GTTAAGGCCA ATAAAAGGTG	3960
CATATTGCCG TCTTTTGGCA ATGTGAGGGC CCGGAAACCT GGCCCTGTCT TCTTGACGAG	4020
GTATAACGGC AGAAAACCGT TACACTCCCG GGCCTTTGGA CCGGGACAGA AGAACTGCTC	4020
CATTCTAGG GGTCTTTCCC CTCTCGCCAA AGGAATGCAA GGTCTGTTGA ATGTCGTGAA	4080
GTAAGGATCC CCAGAAAGGG GAGAGCGGTT TCCTTACGTT CCAGACAACT TACAGCACTT	4080
GGAAGCAGTT CCTCTGGAAG CTTCTTGAAG ACAAACAACG TCTGTAGCGA CCCTTTGCAG	4140
CCTTCGTCAA GGAGACCTC GAAGAACTTC TGTTTGTTC AGACATCGCT GGGAAACGTC	4140
GCAGCGGAAC CCCCCACCTG GCGACAGGTG CCTCTGCGGC CAAAAGCCAC GTGTATAAGA	4200
CGTCGCCTTG GGGGGTGGAC CGCTGTCCAC GGAGACGCCG GTTTTCGGTG CACATATTCT	4200
TACACCTGCA AAGGCGGCAC AACCCAGTG CCACGTTGTG AGTTGGATAG TTGTGGAAAG	4260
ATGTGGACGT TTCCGCCGTG TTGGGGTCAC GGTGCAACAC TCAACCTATC AACACCTTTC	4260
AGTCAAATGG CTCTCCTCAA GCGTATTCAA CAAGGGGCTG AAGGATGCCC AGAAGGTACC	4320
TCAGTTTACC GAGAGGAGTT CGCATAAGTT GTTCCCCGAC TTCCTACGGG TCTTCCATGG	4320
CCATTGTATG GGATCTGATC TGGGGCCTCG GTGCACATGC TTTACATGTG TTTAGTCGAG	4380
GGTAACATAC CCTAGACTAG ACCCCGGAGC CACGTGTACG AAATGTACAC AAATCAGCTC	4380
GTAAAAAAC GTCTAGGCCC CCCGAACCAC GGGGACGTGG TTTTCCTTTG AAAAACACGA	4440
CAATTTTTTG CAGATCCGGG GGGCTTGGTG CCCCTGCACC AAAAGGAAAC TTTTGTGCT	4440
TGATAATACC ATGAAAAAGC CTGAACTCAC CGCGACGTCT GTCGAGAAGT TTCTGATCGA	4500
ACTATTATGG TACTTTTTCG GACTTGAGTG GCGCTGCAGA CAGCTCTTCA AAGACTAGCT	4500
AAAGTTCGAC AGCGTCTCCG ACCTGATGCA GCTCTCGGAG GGCGAAGAAT CTCGTGCTTT	4560
TTTCAAGCTG TCGCAGAGGC TGGACTACGT CGAGAGCCTC CCGCTTCTTA GAGCACGAAA	4560
CAGCTTCGAT GTAGGAGGGC GTGGATATGT CCTGCGGGTA AATAGCTGCG CCGATGGTTT	4620
GTGAAGCTA CATCCTCCCG CACCTATACA GGACGCCCAT TTATCGACGC GGCTACCAAA	4620
CTACAAAGAT CGTTATGTTT ATCGGCACTT TGCATCGGCC GCGCTCCCGA TTCCGGAAGT	4680
GATGTTTCTA GCAATACAAA TAGCCGTGAA ACGTAGCCGG CCGAGGGGCT AAGGCCTTCA	4680

FIG.12B-6



## pICAST OMC

GCTTGACATT GGGGAATTTA GCGAGAGCCT GACCTATTGC ATCTCCCGCC GTGCACAGGG	4740
CGAACTGTAA CCCCTTAAAT CGCRCTCGGA CTGGATAACG TAGAGGGCGG CACGTGTCCC	4740
TGTCACGTTG CAAGACCTGC CTGAAACCGA ACTGCCCCGT GTTCTGCAGC CGGTCGCGGA	4800
ACAGTGCAAC GTTCTGGACG GACTTTGGCT TGACGGGCGA CAAGACGTCG GCCAGCGCCT	4800
GGCCATGGAT GCGATCGCTG CGGCCGATCT TAGCCAGACG AGCGGGTTCG GCCCATTCGG	4860
CCGGTACCTA CGCTAGCGAC GCCGGCTAGA ATCGGTCTGC TCGCCCAAGC CGGGTAAGCC	4860
ACCGCAAGGA ATCGGTCAAT AACTACATG GCGTGATTTT ATATGCGCGA TTGCTGATCC	4920
TGGCGTTCTT TAGCCAGTTA TGTGATGTAC CGCACTAAAG TATACGCGCT AACGACTAGG	4920
CCATGTGTAT CACTGGCAAA CTGTGATGGA CGACACCGTC AGTGCGTCCG TCGCGCAGGC	4980
GGTACACATA GTGACCGTTT GAACTACCT GCTGTGGCAG TCACGCAGGC AGCGCGTCCG	4980
TCTCGATGAG CTGATGCTTT GGGCCGAGGA CTGCCCCGAA GTCCGGCACC TCGTGCACGC	5040
AGAGCTACTC GACTACGAAA CCCGGCTCCT GACGGGGCTT CAGGCCGTGG AGCACGTGCG	5040
GGATTTCCGG TCCAACAATG TCCTGACGGA CAATGGCCGC ATAACAGCGG TCATTGACTG	5100
CCTAAAGCCG AGGTTGTTAC AGGACTGCCT GTTACCGCGG TATTGTGCCG AGTAACTGAC	5100
GAGCGAGGCG ATGTTCCGGG ATTCCCAATA CGAGGTCGCC AACATCTTCT TCTGGAGGCC	5160
CTCGTCCGC TACAAGCCCC TAAGGGTTAT GCTCCAGCGG TTGTAGAAGA AGACCTCCGG	5160
GTGGTTGGCT TGTATGGAGC AGCAGACGCG CTAATTGAG CGGAGGCATC CGGAGCTTGC	5220
CACCAACCGA ACATACCTCG TCGTCTGCGC GATGAAGCTC GCCTCCGTAG GCCTCGAACG	5220
AGGATCGCCG CGGCTCCGGG CGTATATGCT CCGCATTGGT CTTGACCAAC TCTATCAGAG	5280
TCCTAGCGGC GCCGAGGCCC GCATATACGA GCGTAACCA GAACTGCTTG AGATAGTCTC	5280
CTTGGTTGAC GGCAATTTG ATGATGCAGC TTGGGCGCAG GGTCGATGCG ACGCAATCGT	5340
GAACCAACTG CCGTTAAAGC TACTACGTCG AACCCGCGTC CCAGCTACGC TCGTTAGCA	5340
CCGATCCGGA GCCGGGACTG TCGGGCGTAC ACAAATCGCC CGCAGAAGCG CGGCCGTCTG	5400
GGTAGGCCCT CGGCCCTGAC AGCCCGCATG TGTTTAGCGG GCGTCTTCGC GCCGGCAGAC	5400
GACCGATGGC TGTGTAGAAG TACTCGCCGA TAGTGGAAC CGACGCCCCA GCACTCGTCC	5460
CTGGCTACCG ACACATCTTC ATGAGCGGCT ATCACCTTTG GCTGCGGGGT CGTGAGCAGG	5460

FIG. 12B-7

## pICAST OMC

GAGGGCAAAG GAATAGAGTA GATGCCGACC GGGATCTATC GATAAAATAA AAGATTTTAT	5520
CTCCCGTTTC CTTATCTCAT CTACGGCTGG CCCTAGATAG CTATTTTATT TTCTAAAATA	5520
TTAGTCTCCA GAAAAAGGGG GGAATGAAAG ACCCCACCTG TAGGTTTGGC AAGCTAGCTT	5580
AATCAGAGGT CTTTTTCCCC CCTTACTTTC TGGGGTGGAC ATCCAAACCG TTCGATCGAA	5580
AAGTAACGCC ATTTTGCAAG GCATGGAAAA ATACATAACT GAGAATAGAG AAGTTCAGAT	5640
TTCATTGCGG TAAAACGTTC CGTACCTTTT TATGTATTGA CTCTTATCTC TTCAAGTCTA	5640
CAAGGTCAGG AACAGATGGA ACAGCTGAAT ATGGGCCAAA CAGGATATCT GTGGTAAGCA	5700
GTTCCAGTCC TTGTCTACCT TGTCGACTTA TACCCGGTTT GTCCTATAGA CACCATTCGT	5700
GTTCTGCCC CGGCTCAGGG CCAAGAACAG ATGGAACAGC TGAATATGGG CCAAACAGGA	5760
CAAGGACGGG GCCGAGTCCC GGTTCCTGTC TACCTTGTCG ACTTATACCC GGTTCCTCT	5760
TATCTGTGGT AAGCAGTTCC TGCCCCGGCT CAGGGCCAAG AACAGATGGT CCCAGATGC	5820
ATAGACACCA TTCGTCAAGG ACGGGGCCGA GTCCCGGTTT TTGTCTACCA GGGGTCTACG	5820
GGTCCAGCCC TCAGCAGTTT CTAGAGAACC ATCAGATGTT TCCAGGGTGC CCCAAGGACC	5880
CCAGGTCGGG AGTCGTCAA GATCTCTTGG TAGTCTACAA AGGTCCACG GGGTTCCTGG	5880
TGAAATGACC CTGTGCCTTA TTTGAACTAA CCAATCAGTT CGCTTCTCGC TTCTGTTCGC	5940
ACTTTACTGG GACACGGAAT AAATTGATT GGTAGTCAA GCGAAGAGCG AAGACAAGCG	5940
GCGCTTCTGC TCCCCGAGCT CAATAAAGA GCCCACAACC CCTCACTCGG GCGCCAGTC	6000
CGCGAAGACG AGGGGCTCGA GTTATTTTCT CGGGTGTGG GGAGTGAGCC CCGCGGTCAG	6000
CTCCGATTGA CTGAGTCGCC CGGGTACCCG TGTATCCAAT AAACCCTCTT GCAGTTGCAT	6060
GAGGCTAACT GACTCAGCGG GCCCATGGGC ACATAGGTTA TTTGGGAGAA CGTCAACGTA	6060
CCGACTTGTG GTCTCGCTGT TCCTTGGGAG GGTCTCCTCT GAGTGATTGA CTACCCGTCA	6120
GGCTGAACAC CAGAGCGACA AGGAACCCTC CCAGAGGAGA CTCACTAAT GATGGGCAGT	6120
GCGGGGGTCT TTCATTGATG CAGCATGTAT CAAAATTAAT TTGGTTTTTT TTCTTAAGTA	6180
CGCCCCCAGA AAGTAAGTAC GTCGTACATA GTTTTAATTA AACCAAAAAA AAGAATTCAT	6180
TTTACATTAA ATGGCCATAG TTGCATTAAT GAATCGGCCA ACGCGCGGGG AGAGGCGGTT	6240
AAATGTAATT TACCGGTATC AACGTAATTA CTTAGCCGGT TGCGCGCCCC TCTCCGCCAA	6240

FIG.12B-8

## pICAST OMC

TGCGTATTGG CGCTCTTCCG CTCCTCGCT CACTGACTCG CTGCGCTCGG TCGTTCGGCT	6300
ACGCATAACC GCGAGAAGGC GAAGGAGCGA GTGACTGAGC GACGCGAGCC AGCAAGCCGA	6300
GCGGCGAGCG GTATCAGCTC ACTCAAAGGC GGTAATACGG TTATCCACAG AATCAGGGGA	6360
CGCCGCTCGC CATAGTCGAG TGAGTTTCCG CCATTATGCC AATAGGTGTC TTAGTCCCCT	6360
TAACGCAGGA AAGAACATGT GAGCAAAAGG CCAGCAAAAG GCCAGGAACC GTAAAAAGGC	6420
ATTGCGTCCT TTCTTGATACA CTCGTTTTCC GGTCGTTTTT CGGTCCTTGG CATTTTTCCG	6420
CGCGTTGCTG GCGTTTTTCC ATAGGCTCCG CCCCCTGAC GAGCATCACA AAAATCGACG	6480
GCGCAACGAC CGCAAAAAGG TATCCGAGGC GGGGGGACTG CTCGTAGTGT TTTTAGCTGC	6480
CTCAAGTCAG AGGTGGCGAA ACCCGACAGG ACTATAAAGA TACCAGGCGT TTCCCCCTGG	6540
GAGTTCAGTC TCCACCGCTT TGGGCTGTCC TGATATTCT ATGGTCCGCA AAGGGGGACC	6540
AAGTCCCTC GTGCGCTCTC CTGTTCCGAC CCTGCCGCTT ACCGGATACC TGTCCGCCTT	6600
TTCGAGGGAG CACGCGAGAG GACAAGGCTG GGACGGCGAA TGGCCTATGG ACAGGCGGAA	6600
TCTCCCTTCG GGAAGCGTGG CGCTTTCTCA TAGCTCACGC TGTAGGTATC TCAGTTCGGT	6660
AGAGGGAAGC CTTTCGCACC GCGAAAGAGT ATCGAGTGCG ACATCCATAG AGTCAAGCCA	6660
GTAGGTCGTT CGCTCCAAGC TGGGCTGTGT GCACGAACCC CCCGTTGAGC CCGACCGCTG	6720
CATCCAGCAA GCGAGGTTG ACCCGACACA CGTGCTTGGG GGGCAAGTCG GGCTGGCGAC	6720
CGCCTTATCC GGTAAGTATC GTCTTGAGTC CAACCCGGTA AGACACGACT TATCGCCACT	6780
GCGGAATAGG CCATTGATAG CAGAACTCAG GTTGGGCCAT TCTGTGCTGA ATAGCGGTGA	6780
GGCAGCAGCC ACTGGTAACA GGATTAGCAG AGCGAGGTAT GTAGGCGGTG CTACAGAGTT	6840
CCGTCGTCGG TGACCATTGT CCTAATCGTC TCGCTCCATA CATCCGCCAC GATGTCTCAA	6840
CTTGAAGTGG TGGCCTAACT ACGGCTACAC TAGAAGAACA GTATTTGGTA TCTGCGCTCT	6900
GAAC TTCACC ACCGGATTGA TGCCGATGTG ATCTTCTTGT CATAAACCAT AGACGCGAGA	6900
GCTGAAGCCA GTTACCTTCG GAAAAAGAGT TGGTAGCTCT TGATCCGGCA AACAAACCAC	6960
CGACTTCGGT CAATGGAAGC CTTTTTCTCA ACCATCGAGA ACTAGGCCGT TTGTTTGGTG	6960
CGCTGGTAGC GGTGGTTTTT TTGTTTGCAA GCAGCAGATT ACGCGCAGAA AAAAAGGATC	7020
GCGACCATCG CCACCAAAAA AACAAAGTT CGTCGTCTAA TGCAGTCTT TTTTCTAG	7020

FIG.12B-9

## pICAST OMC

TCAAGAAGAT CCTTTGATCT TTTCTACGGG GTCTGACGCT CAGTGGAACG AAAACTCACG	7080
AGTTCTTCTA GGAAACTAGA AAAGATGCCC CAGACTGCGA GTCACCTTGC TTTTGAGTGC	7080
TTAAGGGATT TTGGTCATGA GATTATCAAA AAGGATCTTC ACCTAGATCC TTTTAAATTA	7140
AATTCCCTAA AACCAGTACT CTAATAGTTT TTCCTAGAAG TGGATCTAGG AAAATTTAAT	7140
AAAATGAAGT TTGCGGCCGC AAATCAATCT AAAGTATATA TGAGTAACT TGGTCTGACA	7200
TTTACTTCA AACGCCGGCG TTTAGTTAGA TTTCATATAT ACTCATTTGA ACCAGACTGT	7200
GTTACCAATG CTTAATCAGT GAGGCACCTA TCTCAGCGAT CTGTCTATTT CGTTCATCCA	7260
CAATGGTTAC GAATTAGTCA CTCCGTGGAT AGAGTCGCTA GACAGATAAA GCAAGTAGGT	7260
TAGTTGCCTG ACTCCCCGTC GTGTAGATAA CTACGATACG GGAGGGCTTA CCATCTGGCC	7320
ATCAACGGAC TGAGGGGCAG CACATCTATT GATGCTATGC CCTCCCGAAT GGTAGACCGG	7320
CCAGTGCTGC AATGATACCG CGAGACCCAC GCTCACCGGC TCCAGATTTA TCAGCAATAA	7380
GGTCACGACG TTAATATGGC GCTCTGGGTG CGAGTGGCCG AGGTCTAAAT AGTCGTTATT	7380
ACCAGCCAGC CGGAAGGGCC GAGCGCAGAA GTGGTCCTGC AACTTTATCC GCCTCCATCC	7440
TGGTCGGTCG GCCTTCCCGG CTCGCGTCTT CACCAGGACG TTGAAATAGG CGGAGGTAGG	7440
AGTCTATTAA TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC GCCAGTTAAT AGTTTGCGCA	7500
TCAGATAATT AACAACGGCC CTTGATCTC ATTCATCAAG CGGTCAATTA TCAAACGCGT	7500
ACGTTGTTGC CATTGCTACA GGCATCGTGG TGTCACGCTC GTCGTTTGGT ATGGCTTCAT	7560
TGCAACAACG GTAACGATGT CCGTAGCACC ACAGTGCGAG CAGCAAACCA TACCGAAGTA	7560
TCAGCTCCGG TTCCAACGA TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAG	7620
AGTCGAGGCC AAGGGTTGCT AGTTCCGCTC AATGTACTAG GGGGTACAAC ACGTTTTTTC	7620
CGGTTAGCTC CTTCCGGTCCT CCGATCGTTG TCAGAAGTAA GTTGCCGCA GTGTTATCAC	7680
GCCAATCGAG GAAGCCAGGA GGCTAGCAAC AGTCTTCATT CAACCGGCGT CACAATAGTG	7680
TCATGGTTAT GGCAGCACTG CATAATTCTC TTAATGTCAT GCCATCCGTA AGATGCTTTT	7740
AGTACCAATA CCGTCGTGAC GTATTAAGAG AATGACAGTA CGGTAGGCAT TCTACGAAAA	7740
CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT	7800
GACACTGACC ACTCATGAGT TGGTTCAGTA AGACTCTTAT CACATACGCC GCTGGCTCAA	7800

FIG.12B-10

## pICAST OMC

GCTCTTGCCC GGC GTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC	7860
CGAGAACGGG CCGCAGTTAT GCCCTATTAT GGC GCGGTGT ATCGTCTTGA AATTTTCACG	7860
TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT	7920
AGTAGTAACC TTTTGCAAGA AGCCCCGCTT TTGAGAGTTC CTAGAATGGC GACAACTCTA	7920
CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA	7980
GGTCAAGCTA CATTGGGTGA GCACGTGGGT TGACTAGAAG TCGTAGAAAA TGAAAGTGGT	7980
GC GTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA	8040
CGCAAAGACC CACTCGTTTT TGTCTTCCG TTTTACGGCG TTTTTCCT TATTCCTGCT	8040
CACGGAAATG TTGAATACTC ATACTCTTCC TTTTCAATA TTATTGAAGC ATTTATCAGG	8100
GTGCCTTTAC AACTTATGAG TATGAGAAGG AAAAAGTTAT AATAACTTCG TAAATAGTCC	8100
GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGG	8160
CAATAACAGA GTA CTGCT ATGTATAAAC TTACATAAAT CTTTTATT TTTATCCCC	8160
TTCCGCGCAC ATTC	8175
AAGGCGCGTG TAAAG	8175

FIG.12B-11

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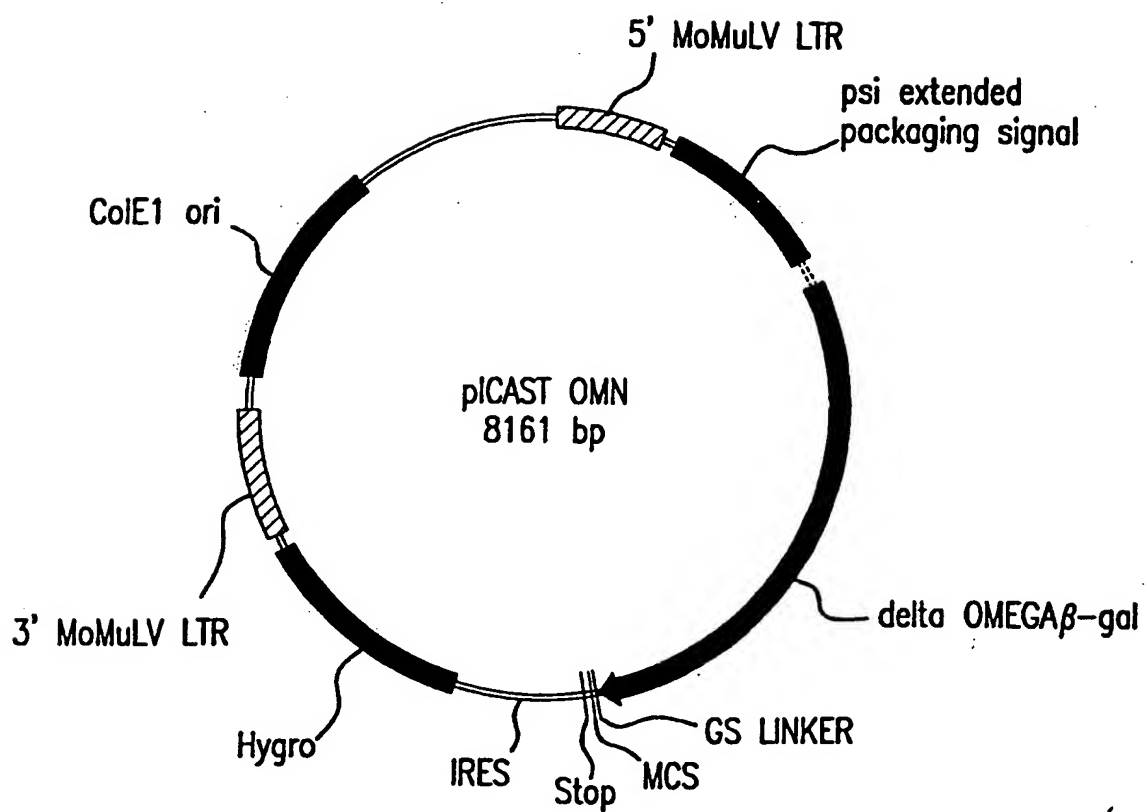


FIG.13A

## pICAST OMN

CTGCAGCCTG AATATGGGCC AAACAGGATA TCTGTGGTAA GCAGTTCCTG CCCC GGCTCA	60
GACGTCGGAC TTATACCCGG TTTGTCCTAT AGACACCATT CGTCAAGGAC GGGGCCGAGT	60
GGGCCAAGAA CAGATGGAAC AGCTGAATAT GGGCCAAACA GGATATCTGT GGTAAGCAGT	120
CCCGGTTCTT GTCTACCTTG TCGACTTATA CCCGGTTTGT CCTATAGACA CCATTCGTCA	120
TCCTGCCCCG GCTCAGGGCC AAGAACAGAT GGTCCCCAGA TCGGTCCAG CCCTCAGCAG	180
AGGACGGGGC CGAGTCCCGG TTCTTGCTA CCAGGGGTCT ACGCCAGGTC GGGAGTCGTC	180
TTTCTAGAGA ACCATCAGAT GTTCCAGGG TGCCCCAAGG ACCTGAAATG ACCCTGTGCC	240
AAAGATCTCT TGGTAGTCTA CAAAGGTCCC ACGGGGTTC TGGACTTTAC TGGGACACGG	240
TTATTTGAAC TAACCAATCA GTTCGCTTCT CGCTTCTGTT CGCGCGCTTC TGCTCCCCGA	300
AATAAACTG ATTGGTTAGT CAAGCGAAGA GCGAAGACAA GCGCGCAAG ACGAGGGGCT	300
GCTCAATAAA AGAGCCCACA ACCCTCACT CGGGGCGCCA GTCCTCCGAT TGA CTGAGTC	360
CGAGTTATTT TCTCGGGTGT TGGGGAGTGA GCCCCGCGGT CAGGAGGCTA ACTGACTCAG	360
GCCCGGGTAC CCGTGTATCC AATAAACCTT CTTGCAGTTG CATCCGACTT GTGGTCTCGC	420
CGGGCCCATG GGCACATAGG TTATTTGGGA GAACGTCAAC GTAGGCTGAA CACCAGAGCG	420
TGTTCTTGG GAGGGTCTCC TCTGAGTGAT TGA CTACCCG TCAGCGGGGG TCTTTCATTT	480
ACAAGGAACC CTCCAGAGG AGACTCACTA ACTGATGGGC AGTCGCCCC AGAAAGTAAA	480
GGGGGCTCGT CCGGGATCGG GAGACCCCTG CCCAGGGACC ACCGACCCAC CACCGGGAGG	540
CCCCGAGCA GGCCTAGCC CTCTGGGGAC GGGTCCCTGG TGGCTGGGTG GTGGCCCTCC	540
CAAGCTGGCC AGCAACTTAT CTGTGTCTGT CCGATTGTCT AGTGTCTATG ACTGATTTTA	600
GTTCGACCGG TCGTTGAATA GACACAGACA GGCTAACAGA TCACAGATAC TGA CTAAAAT	600
TGCGCCTGCG TCGGTACTAG TTAGCTAACT AGCTCTGTAT CTGGCGGACC CGTGGTGGAA	660
ACGCGGACGC AGCCATGATC AATCGATTGA TCGAGACATA GACCGCCTGG GCACCACTT	660
CTGACGAGTT CTGAACACCC GGCCGCAACC CTGGGAGACG TCCCAGGGAC TTTGGGGGCC	720
GACTGCTCAA GACTTGTGGG CCGGCGTTGG GACCCTCTGC AGGGTCCCTG AAACCCCGG	720
GTTTTTGTGG CCCGACCTGA GGAAGGGAGT CGATGTGGAA TCCGACCCCG TCAGGATATG	780
CAAAAACACC GGGCTGGACT CCTTCCCTCA GCTACACCTT AGGCTGGGGC AGTCTATAC	780

FIG. 13B-1

## pICAST OMN

TGGTTCTGGT AGGAGACGAG AACCT/AAAC AGTTCCCGCC TCCGTCTGAA TTTTGTCTTT	840
ACCAAGACCA TCCTCTGCTC TTGGATTTTG TCAAGGGCGG AGGCAGACTT AAAAACGAAA	840
CGGTTTGGAA CCGAAGCCGC GCGTCTTGTC TGCTGCAGCA TCGTTCTGTG TTGTCTCTGT	900
GCCAAACCTT GGCTTCGGCG CGCAGAACAG ACGACGTCGT AGCAAGACAC AACAGAGACA	900
CTGACTGTGT TTCTGTATTT GTCTGAAAAT TAGGGCCAGA CTGTTACCAC TCCCTTAAGT	960
GACTGACACA AAGACATAAA CAGACTTTTA ATCCCGGTCT GACAATGGTG AGGGAATTCA	960
TTGACCTTAG GTAACCTGGAA AGATGTCGAG CGGCTCGCTC ACAACCAGTC GGTAGATGTC	1020
AACTGGAATC CATTGACCTT TCTACAGCTC GCCGAGCGAG TGTTGGTCAG CCATCTACAG	1020
AAGAAGAGAC GTTGGGTTAC CTTCTGCTCT GCAGAATGGC CAACCTTTAA CGTCGGATGG	1080
TTCTTCTCTG CAACCCAATG GAAGACGAGA CGTCTTACCG GTTGGAAATT GCAGCCTACC	1080
CCGCGAGACG GCACCTTTAA CCGAGACCTC ATCACCAGG TTAAGATCAA GGTCTTTTCA	1140
GGCGCTCTGC CGTGGAATT GGCTCTGGAG TAGTGGGTCC AATTCTAGTT CCAGAAAAGT	1140
CCTGGCCCGC ATGGACACCC AGACCAGGTC CCCTACATCG TGACCTGGGA AGCCTTGGCT	1200
GGACCGGGCG TACCTGTGGG TCTGGTCCAG GGGATGTAGC ACTGGACCCT TCGGAACCGA	1200
TTTGACCCCC CTCCTGGGT CAAGCCCTTT GTACACCCTA AGCCTCCGCC TCCTCTTCCT	1260
AAACTGGGGG GAGGGACCCA GTTCGGGAAA CATGTGGGAT TCGGAGGCGG AGGAGAAGGA	1260
CCATCCGCCC CGTCTCTCCC CTTGAACCT CTCGTTTCA CCCCCTCG ATCCTCCCTT	1320
GGTAGGCGGG GCAGAGAGGG GGAACCTTGA GGAGCAAGCT GGGGCGGAGC TAGGAGGGAA	1320
TATCCAGCCC TACTCCTTC TCTAGGCGCC GGCCGCTCTA GCCATTAAT ACGACTCACT	1380
ATAGGTCGGG AGTGAGGAAG AGATCCGCGG CCGGCGAGAT CGGGTAATTA TGCTGAGTGA	1380
ATAGGGCGAT TCGAACACCA TGCACCATCA TCATCATCAC GTCGACGAAC AGAAACTCAT	1440
TATCCCGCTA AGCTTGTTGGT ACGTGGTAGT AGTAGTAGTG CAGCTGCTTG TCTTTGAGTA	1440
TTCCGAAGAA GACCTACTCG AGATGGGCGT GATTACGGAT TACTGGCCG TCGTTTTACA	1500
AAGGCTTCTT CTGGATGAGC TCTACCGCA CTAATGCCTA AGTGACCGGC AGCAAAATGT	1500
ACGTCGTGAC TGGGAAAACC CTGGCGTTAC CCAACTTAAT CGCCTTGACG CACATCCCC	1560
TGCAGCACTG ACCCTTTTGG GACCGCAATG GGTGAATTA GCGGAACGTC GTGTAGGGGG	1560

FIG.13B-2



## pICAST OMN

TTTCGCCAGC TGGCGTAATA GCGAAGAGGC CCGCACCGAT CGCCCTTCCC AACAGTTACG	1620
AAAGCGGTGC ACCGCATTAT CGCTTCTCCG GCGTGGCTA GCGGGAAGGG TTGTCAATGC	1620
CAGCCTGAAT GCGAATGGC GCTTTGCCTG GTTTCGGCA CCAGAAGCGG TGCCGAAAG	1680
GTCGGACTTA CCGCTTACCG CGAAACGGAC CAAAGGCCGT GGTCTTCGCC ACGGCCTTTC	1680
CTGGCTGGAG TGCGATCTTC CTGAGGCCGA TACTGTCGTC GTCCCTCAA ACTGGCAGAT	1740
GACCGACCTC ACGCTAGAAG GACTCCGGCT ATGACAGCAG CAGGGGAGTT TGACCGTCTA	1740
GCACGGTTAC GATGCGCCCA TCTACACCAA CGTGACCTAT CCCATTACGG TCAATCCGCC	1800
CGTGCCAATG CTACGCGGGT AGATGTGGTT GCACTGGATA GGGTAATGCC AGTTAGGCGG	1800
GTTTGTTCCC ACGGAGAATC CGACGGGTTG TTA CTGCTC ACATTTAATG TTGATGAAAG	1860
CAAACAAGGG TGCCTCTTAG GCTGCCAAC AATGAGCGAG TGTAATTAC AACTACTTTC	1860
CTGGCTACAG GAAGGCCAGA CGCGAATTAT TTTTGATGGC GTTAACTCGG CGTTTCATCT	1920
GACCGATGTC CTTCCGGTCT GCGCTTAATA AAAACTACCG CAATTGAGCC GCAAAGTAGA	1920
GTGGTGCAAC GGGCGCTGGG TCGGTTACGG CCAGGACAGT CGTTTGCCGT CTGAATTTGA	1980
CACCACGTTG CCCGCGACCC AGCCAATGCC GGTCTGTCA GCAAACGGCA GACTTAACT	1980
CCTGAGCGCA TTTTACGCG CCGGAGAAAA CCGCCTCGCG GTGATGGTGC TCGCTGGAG	2040
GGA CTGCGT AAAAATGCGC GGCCTCTTTT GCGGAGCGC CACTACCAG ACGCGACCTC	2040
TGACGGCAGT TATCTGGAAG ATCAGGATAT GTGGCGGATG AGCGGCATTT TCCGTGACGT	2100
ACTGCCGTCA ATAGACCTTC TAGTCCTATA CACCGCCTAC TCGCCGTAA AGGCACTGCA	2100
CTCGTTGCTG CATAAACCGA CTACACAAAT CAGCGATTTC CATGTTGCCA CTCGCTTTAA	2160
GAGCAACGAC GTATTTGGCT GATGTGTTTA GTCGCTAAAG GTACAACGGT GAGCGAAATT	2160
TGATGATTTT AGCCGCGCTG TACTGGAGGC TGAAGTTCAG ATGTGCGGCG AGTTGCGTGA	2220
ACTACTAAAG TCGGCGCGAC ATGACCTCCG ACTTCAAGTC TACACGCCG TCAACGCACT	2220
CTACCTACGG GTAACAGTTT CTTTATGGCA GGGTGAAACG CAGGTCGCCA GCGGCACCGC	2280
GATGGATGCC CATTGTCAAA GAAATACCGT CCCACTTTGC GTCCAGCGGT CGCCGTGGCG	2280
GCCTTTCGGC GGTGAAATTA TCGATGAGCG TGGTGGTTAT GCCGATCGCG TCACACTACG	2340
CGGAAAGCCG CCACTTTAAT AGCTACTCGC ACCACCAATA CGGCTAGCGC AGTGTGATGC	2340

FIG. 13B-3

## pICAST OMN

TCTGAACGTC	GAAAACCCGA	AACTGTGGAG	CGCCGAAATC	CCGAATCTCT	ATCGTGCGGT	2400
AGACTTGACG	CTTTTGGGCT	TTGACACCTC	GCGGCTTTAG	GGCTTAGAGA	TAGCACGCCA	2400
GGTTGAACTG	CACACCGCCG	ACGGCACGCT	GATTGAAGCA	GAAGCCTGCG	ATGTCGGTTT	2460
CCAACTTGAC	GTGTGGCGGC	TGCCGTGCCA	CTAACTTCGT	CTTCGGACGC	TACAGCCAAA	2460
CCGCGAGGTG	CGGATTGAAA	ATGGTCTGCT	GCTGCTGAAC	GGCAAGCCGT	TGCTGATTCTG	2520
GGCGCTCCAC	GCCTAACTTT	TACCAGACGA	CGACGACTTG	CCGTTCCGCA	ACGACTAAGC	2520
AGGCGTTAAC	CGTCACGAGC	ATCATCCTCT	GCATGGTCAG	GTCATGGATG	AGCAGACGAT	2580
TCCGCAATTG	GCAGTGCTCG	TAGTAGGAGA	CGTACCAGTC	CAGTACCTAC	TCGTCTGCTA	2580
GGTGCAGGAT	ATCCTGCTGA	TGAAGCAGAA	CAACTTTAAC	GCCGTGCGCT	GTTTCGCTTA	2640
CCACGTCCTA	TAGGACGACT	ACTTCGTCTT	GTTGAAATTG	CGGCACGCGA	CAAGCGTAAT	2640
TCCGAACCAT	CCGCTGTGGT	ACACGCTGTG	CGACCGCTAC	GGCCTGTATG	TGGTGGATGA	2700
AGGCTTGGTA	GGCGACACCA	TGTGCGACAC	GCTGGCGATG	CCGGACATAC	ACCACCTACT	2700
AGCCAATATT	GAAACCCACG	GCATGGTGCC	AATGAATCGT	CTGACCGATG	ATCCGCGCTG	2760
TCGGTTATAA	CTTTGGGTGC	CGTACCACGG	TTACTTAGCA	GACTGGCTAC	TAGGCGCGAC	2760
GCTACCGGCG	ATGAGCGAAC	GCGTAACGCG	AATGGTGCAG	CGCGATCGTA	ATCACCCGAG	2820
CGATGGCCGC	TACTCGCTTG	CGCATTGCGC	TTACCACGTC	GCGCTAGCAT	TAGTGGGCTC	2820
TGTGATCATC	TGGTCGCTGG	GGAATGAATC	AGGCCACGGC	GCTAATCACG	ACGCGCTGTA	2880
ACACTAGTAG	ACCAGCGACC	CCTTACTTAG	TCCGGTGCCG	CGATTAGTGC	TGCGCGACAT	2880
TCGCTGGATC	AAATCTGTCTG	ATCCTTCCCG	CCCGGTGCAG	TATGAAGGCG	GCGGAGCCGA	2940
AGCGACCTAG	TTAGACAGC	TAGGAAGGGC	GGGCCACGTC	ATACTTCCGC	CGCCTCGGCT	2940
CACCACGGCC	ACCGATATTA	TTTGCCCGAT	GTACGCGCGC	GTGGATGAAG	ACCAGCCCTT	3000
GTGGTGCCGG	TGGCTATAAT	AAACGGGCTA	CATGCGCGCG	CACCTACTTC	TGGTCGGGAA	3000
CCCGGCTGTG	CCGAAATGGT	CCATCAAAAA	ATGGCTTTCTG	CTACCTGGAG	AGACGCGCCC	3060
GGGCCGACAC	GGCTTTACCA	GGTAGTTTTT	TACCGAAAGC	GATGGACCTC	TCTGCGCGGG	3060
GCTGATCCTT	TGCGAATACG	CCCACGCGAT	GGGTAACAGT	CTTGGCGGTT	TCGCTAAATA	3120
CGACTAGGAA	ACGCTTATGC	GGGTGCGCTA	CCCATTTGTC	GAACCGCCAA	AGCGATTTAT	3120

FIG. 13B-4

## pICAST OMN

CTGGCAGGCG TTTCGTCAGT ATCCCCGTTT ACAGGGCGGC TTCGTCTGGG ACTGGGTGGA	3180
GACCGTCCGC AAAGCAGTCA TAGGGGCAAA TGTCCCGCCG AAGCAGACCC TGACCCACCT	3180
TCAGTCGCTG ATTAATATG ATGAAAACGG CAACCCGTGG TCGGCTTACG GCGGTGATTT	3240
AGTCAGCGAC TAATTTATAC TACTTTTGCC GTTGGGCACC AGCCGAATGC CGCCACTAAA	3240
TGGCGATACG CCGAACGATC GCCAGTTCTG TATGAACGGT CTGGTCTTTG CCGACCGCAC	3300
ACCGCTATGC GGCTTGCTAG CGGTCAAGAC ATACTTGCCA GACCAGAAAC GGCTGGCGTG	3300
GCCGCATCCA GCGCTGACGG AAGCAAAACA CCAGCAGCAG TTTTCCAGT TCCGTTTATC	3360
CGGCGTAGGT CGGACTGCC TTCGTTTTGT GGTCGTCGTC AAAAAGGTCA AGGCAAATAG	3360
CGGGCAAACC ATCGAAGTGA CCAGCGAATA CCTGTTCCGT CATAGCGATA ACGAGCTCCT	3420
GCCCCTTTGG TAGCTTCACT GGTCGCTTAT GGACAAGGCA GTATCGCTAT TGCTCGAGGA	3420
GCACTGGATG GTGGCGCTGG ATGGTAAGCC GCTGGCAAGC GGTGAAGTGC CTCTGGATGT	3480
CGTGACCTAC CACCGCGACC TACCATTCCG CGACCGTTCC CCACTTCACG GAGACCTACA	3480
CGCTCCACAA GGTAACAGT TGATTGAACT GCCTGAACTA CCGCAGCCGG AGAGCGCCGG	3540
GCGAGGTGTT CCATTTGTCA ACTAATTGA CGGACTTGAT GCGTCGGCC TCTCGCGGCC	3540
GCAACTCTGG CTCACAGTAC GCGTAGTGCA ACCGAACGCG ACCGCATGGT CAGAAGCCGG	3600
CGTTGAGACC GAGTGTGATG CGCATCACGT TGGCTTGCGC TGGCGTACCA GTCTTCGGCC	3600
GCACATCAGC GCCTGGCAGC AGTGGCGTCT GGCGGAAAAC CTCAGTGTGA CGCTCCCCGC	3660
CGTGTAGTCG CGGACCGTCG TCACCGCAGA CCGCCTTTTG GAGTCACACT GCGAGGGGCG	3660
CGCGTCCCAC GCCATCCCGC ATCTGACCAC CAGCGAAATG GATTTTGTGA TCGAGCTGGG	3720
GCGCAGGGTG CGGTAGGGCG TAGACTGGTG GTCGCTTTAC CTA AAAACGT AGCTCGACCC	3720
TAATAAGCGT TGGCAATTTA ACCGCCAGTC AGGCTTTCTT TCACAGATGT GGATTGGCGA	3780
ATTATTCGCA ACCGTAAAT TGGCGGTCAG TCCGAAAGAA AGTGTCTACA CCTAACCGCT	3780
TAAAAACAA CTGCTGACGC CGCTGCGCGA TCAGTTCACC CGTGTCGATA GATCTGGAGG	3840
ATTTTTTGTT GACGACTGCG GCGACGCGCT AGTCAAGTGG GCACAGCTAT CTAGACCTCC	3840
TGGTGGCAGC AGGCCTTGGC GCGCCGATC CTTAATTAAC AATTGACCGG TAATAATAGG	3900
ACCACCGTCG TCCGGAACCG CGCGGCCTAG GAATTAATTG TTAAGTGGCC ATTATTATCC	3900

FIG. 13B-5

## pICAST OMN

TAGATAAGTG ACTGATTAGA TGCATTTCTGA CTAGATCCCT CGACCAATTC CGGTTATTTT	3960
ATCTATTAC TGAATAATCT ACGTAAAGCT GATCTAGGGA GCTGGTTAAG GCCAATAAAA	3960
CCACCATATT GCCGTCTTTT GGCAATGTGA GGGCCCGGAA ACCTGGCCCT GTCTTCTTGA	4020
GGTGGTATAA CGGCAGAAAA CCGTTACACT CCCGGGCCTT TGGACCGGGA CAGAAGAACT	4020
CGAGCATTCC TAGGGGTCTT TCCCCTCTCG CCAAAGGAAT GCAAGGTCTG TTGAATGTCG	4080
GCTCGTAAGG ATCCCCAGAA AGGGGAGAGC GGTTCCTTA CGTTCAGAC AACTTACAGC	4080
TGAAGGAAGC AGTTCCTCTG GAAGCTTCTT GAAGACAAAC AACGTCTGTA GCGACCCTTT	4140
ACTTCCTTCG TCAAGGAGAC CTTTGAAGAA CTTCTGTTTG TTGCAGACAT CGCTGGGAAA	4140
GCAGGCAGCG GAACCCCCCA CCTGGCGACA GGTGCCTCTG CGGCCAAAAG CCACGTGTAT	4200
CGTCCGTCGC CTTGGGGGGT GGACCGCTGT CCACGGAGAC GCCGGTTTTT GGTGCACATA	4200
AAGATACACC TGCAAAGGCG GCACAACCCC AGTGCCACGT TGTGAGTTGG ATAGTTGTGG	4260
TTCTATGTGG ACGTTTCCGC CGTGTGGGG TCACGGTGCA ACACTCAACC TATCAACACC	4260
AAAGAGTCAA ATGGCTCTCC TCAAGCGTAT TCAACAAGGG GCTGAAGGAT GCCCAGAAGG	4320
TTTCTCAGTT TACCGAGAGG AGTTCGCATA AGTTGTTCCC CGACTTCCTA CGGGTCTTCC	4320
TACCCCATTTG TATGGGATCT GATCTGGGGC CTCGGTGAC ATGCTTTACA TGTGTTTAGT	4380
ATGGGGTAAC ATACCCTAGA CTAGACCCCG GAGCCACGTG TACGAAATGT ACACAAATCA	4380
CGAGGTAAAA AAACGTCTAG GCCCCCGAA CCACGGGGAC GTGGTTTTCC TTGAAAAAC	4440
GCTCCAATTT TTTGCAGATC CGGGGGGCTT GGTGCCCTG CACCAAAAGG AAACTTTTTG	4440
ACGATGATAA TACCATGAAA AAGCCTGAAC TCACCGCGAC GTCTGTGAG AAGTTTCTGA	4500
TGCTACTATT ATGGTACTTT TTCGGACTTG AGTGGCGCTG CAGACAGCTC TTCAAAGACT	4500
TCGAAAAGTT CGACAGCGTC TCCGACCTGA TGCAGCTCTC GGAGGGCGAA GAATCTCGTG	4560
AGCTTTTCAA GCTGTGCGAG AGGCTGGACT ACGTCGAGAG CCTCCCGCTT CTTAGAGCAC	4560
CTTTCAGCTT CGATGTAGGA GGGCGTGGAT ATGTCCTGCG GGTAAATAGC TGCGCCGATG	4620
GAAAGTCGAA GCTACATCCT CCCGCACCTA TACAGGACGC CCAATTATCG ACGCGGCTAC	4620
GTTTCTACAA AGATCGTTAT GTTTATCGGC ACTTTGCATC GGCCGCGCTC CCGATTCCGG	4680
CAAAGATGTT TCTAGCAATA CAAATAGCCG TGAAACGTAG CCGGCGCGAG GGCTAAGGCC	4680

FIG. 13B-6

## pICAST OMN

AAGTGCTTGA CATTGGGGAA TTTAGCGAGA GCCTGACCTA TTGCATCTCC CGCCGTGCAC	4740
TTCACGAACT GTAACCCCTT AAATCGCTCT CGGACTGGAT AACGTAGAGG GCGGCACGTG	4740
AGGGTGTCAC GTTGCAAGAC CTGCCTGAAA CCGAACTGCC CGCTGTTCTG CAGCCGGTCTG	4800
TCCCACAGTG CAACGTTCTG GACGGACTTT GGCTTGACGG GCGACAAGAC GTCGGCCAGC	4800
CGGAGGCCAT GGATGCGATC GCTGCGGCCG ATCTTAGCCA GACGAGCGGG TTCGGCCCAT	4860
GCCTCCGGTA CCTACGCTAG CGACGCCGGC TAGAATCGGT CTGCTCGCCC AAGCCGGGTA	4860
TCGGACCGCA AGGAATCGGT CAATACACTA CATGGCGTGA TTTCATATGC GCGATTGCTG	4920
AGCCTGGCGT TCCTTAGCCA GTTATGTGAT GTACCGCACT AAAGTATACG CGCTAACGAC	4920
ATCCCCATGT GTATCACTGG CAACTGTGA TGGACGACAC CGTCAGTGCG TCCGTCGCGC	4980
TAGGGGTACA CATAGTGACC GTTTGACACT ACCTGCTGTG GCAGTCACGC AGGCAGCGCG	4980
AGGCTCTCGA TGAGCTGATG CTTTGGGCCG AGGACTGCCC CGAAGTCCGG CACCTCGTGC	5040
TCCGAGAGCT ACTCGACTAC GAAACCCGGC TCCTGACGGG GCTTCAGGCC GTGGAGCACG	5040
ACGCGGATTT CGGCTCCAAC AATGTCCTGA CGGACAATGG CCGCATAACA GCGGTCATTG	5100
TGCGCCTAAA GCCGAGGTTG TTACAGGACT GCCTGTTACC GCGTATTGT CGCCAGTAAC	5100
ACTGGAGCGA GGCATGTTT GGGGATTCCC AATACGAGGT CGCCAACATC TTCTTCTGGA	5160
TGACCTCGCT CCGCTACAAG CCCCTAAGGG TTATGCTCCA GCGGTTGTAG AAGAAGACCT	5160
GGCCGTGGTT GGCTTGATG GAGCAGCAGA CGCGCTACTT CGAGCGGAGG CATCCGGAGC	5220
CCGGCACCAA CCGAACATAC CTCGTCGTCT GCGCGATGAA GCTCGCCTCC GTAGGCCTCG	5220
TTGCAGGATC GCCGCGGCTC CGGGCGTATA TGCTCCGCAT TGGTCTTGAC CAACTCTATC	5280
AACGTCCTAG CGGCGCCGAG GCCCGCATAT ACGAGGCGTA ACCAGAACTG GTTGAGATAG	5280
AGAGCTTGGT TGACGGCAAT TTCGATGATG CAGCTTGGGC GCAGGGTCGA TGCACGCAA	5340
TCTCGAACCA ACTGCCGTTA AAGCTACTAC GTCGAACCCG CGTCCAGCT ACGCTGCGTT	5340
TCGTCCGATC CGGAGCCGGG ACTGTCGGGC GTACACAAAT CGCCCGCAGA AGCGCGGCCG	5400
AGCAGGCTAG GCCTCGGCCC TGACAGCCCG CATGTGTTTA GCGGGCGTCT TCGCGCCGGC	5400
TCTGGACCGA TGGCTGTGTA GAAGTACTCG CCGATAGTGG AAACCGACGC CCCAGCACTC	5460
AGACCTGGCT ACCGACACAT CTTCATGAGC GGCTATCACC TTTGGCTGCG GGGTCGTGAG	5460

FIG. 13B-7

## pICAST OMN

GTCCGAGGGC AAAGGAATAG AGTAGATGCC GACCGGGATC TATCGATAAA ATAAAAGATT	5520
CAGGCTCCCG TTTCCTTATC TCATCTACGG CTGGCCCTAG ATAGCTATTT TATTTTCTAA	5520
TTATTTAGTC TCCAGAAAAA GGGGGGAATG AAGACCCCAA CCTGTAGGTT TGGCAAGCTA	5580
AATAATCAG AGGTCTTTTT CCCCCCTTAC TTCTGGGGT GGACATCCAA ACCGTTGAT	5580
GCTTAAGTAA CGCCATTTTG CAAGGCATGG AAAAATACAT AACTGAGAAT AGAGAAGTTC	5640
CGAATTCATT GCGGTAAAC GTTCCGTACC TTTTATGTA TTGACTCTTA TCTCTCAAG	5640
AGATCAAGGT CAGGAACAGA TGAACAGCT GAATATGGGC CAAACAGGAT ATCTGTGGTA	5700
TCTAGTTCCA GTCCTTGTCT ACCTTGTGCA CTTATACCG GTTTGTCCTA TAGACACCAT	5700
AGCAGTTCCT GCCCCGGCTC AGGGCCAAGA ACAGATGGAA CAGCTGAATA TGGGCCAAAC	5760
TCGTCAAGGA CGGGGCCGAG TCCCGGTTCT TGTCTACCTT GTCGACTTAT ACCCGGTTTG	5760
AGGATATCTG TGGTAAGCAG TTCCTGCCCC GGCTCAGGGC CAAGAACAGA TGGTCCCCAG	5820
TCCTATAGAC ACCATTCGTC AAGGACGGGG CCGAGTCCCG GTTCTTGTCT ACCAGGGGTC	5820
ATGCGGTCCA GCCCTCAGCA GTTTCTAGAG AACCATCAGA TGTTTCCAGG GTGCCCAAG	5880
TACGCCAGGT CGGGAGTCGT CAAAGATCTC TTGGTAGTCT ACAAAGGTCC CACGGGGTTC	5880
GACCTGAAAT GACCCTGTGC CTTATTTGAA CTAACCAATC AGTTCGCTTC TCGCTTCTGT	5940
CTGGACTTTA CTGGGACACG GAATAAACTT GATTGGTTAG TCAAGCGAAG AGCGAAGACA	5940
TCGCGCGCTT CTGCTCCCCG AGCTCAATAA AAGAGCCCAC AACCCCTCAC TCGGGGCGCC	6000
AGCGCGCGAA GACGAGGGGC TCGAGTTATT TTCTCGGGTG TTGGGGAGTG AGCCCCGCGG	6000
AGTCCTCCGA TTGACTGAGT CGCCCGGGTA CCCGTGTATC CAATAAACCC TCTTGCAGTT	6060
TCAGGAGGCT AACTGACTCA GCGGGCCCAT GGGCACATAG GTTATTTGGG AGAACGTCAA	6060
GCATCCGACT TGTGGTCTCG CTGTTCTTG GGAGGGTCTC CTCTGAGTGA TTGACTACCC	6120
CGTAGGCTGA ACACCAGAGC GACAAGGAAC CCTCCAGAG GAGACTCACT AACTGATGGG	6120
GTCAGCGGGG GTCTTTCATT CATGCAGCAT GTATCAAAT TAATTTGGTT TTTTCTTA	6180
CAGTCGCCCC CAGAAAGTAA GTACGTCGTA CATAGTTTTA ATTAACCAA AAAAAAGAA	6180
AGTATTTACA TTAAATGGCC ATAGTTGCAT TAATGAATCG GCCAACGCGC GGGGAGAGGC	6240
TCATAAATGT AATTTACCGG TATCAACGTA ATTACTTAGC CGGTTGCGCG CCCCTCTCCG	6240

FIG. 13B-8

## pICAST OMN

GGTTTGCCTA TTGGCGCTCT TCCGCTTCCT CGCTCACTGA CTCGCTGCGC TCGGTCGTTT	6300
CCAAACGCAT AACC GCGAGA AGGCGAAGGA GCGAGTGA CT GAGCGACGCG AGCCAGCAAG	6300
GGCTGCGGCG AGCGGTATCA GCTCACTCAA AGGCGGTAAT ACGGTTATCC ACAGAATCAG	6360
CCGACGCCGC TCGCCATAGT CGAGTGAGTT TCCGCCATTA TGCCAATAGG TGTCTTAGTC	6360
GGGATAACGC AGGAAAGAAC ATGTGAGCAA AAGGCCAGCA AAAGGCCAGG AACCGTAAAA	6420
CCCTATTGCG TCCTTTCTTG TACACTCGTT TTCCGGTCGT TTTCCGGTCC TTGGCATTTC	6420
AGGCCGCGTT GCTGGCGTTT TTCCATAGGC TCCGCCCCC TGACGAGCAT CACAAAAATC	6480
TCCGGCGCAA CGACCGCAA AAGGTATCCG AGGCGGGGGG ACTGCTCGTA GTGTTTTTAG	6480
GACGCTCAAG TCAGAGGTGG CGAAACCCGA CAGGACTATA AAGATACCAG GCGTTTCCCC	6540
CTGCGAGTTC AGTCTCCACC GCTTTGGGCT GTCCTGATAT TTCTATGGTC CGCAAAGGGG	6540
CTGGAAGCTC CCTCGTGCGC TCTCCTGTTT CGACCCTGCC GCTTACCGGA TACCTGTCCG	6600
GACCTTCGAG GGAGCACGCG AGAGGACAAG GCTGGGACGG CGAATGGCCT ATGGACAGGC	6600
CCTTTCTCCC TTCGGGAAGC GTGGCGCTTT CTCATAGCTC ACGCTGTAGG TATCTCAGTT	6660
GGAAAGAGGG AAGCCCTTCG CACCGCGAAA GAGTATCGAG TGCGACATCC ATAGAGTCAA	6660
CGGTGTAGGT CGTTCGCTCC AAGCTGGGCT GTGTGCACGA ACCCCCCGTT CAGCCCGACC	6720
GCCACATCCA GCAAGCGAGG TTCGACCCGA CACACGTGCT TGGGGGGCAA GTCGGGCTGG	6720
GCTGCGCCTT ATCCGGTAAC TATCGTCTTG AGTCCAACCC GGTAAGACAC GACTTATCGC	6780
CGACGCGGAA TAGGCCATTG ATAGCAGAAC TCAGGTTGGG CCATTCTGTG CTGAATAGCG	6780
CACTGGCAGC AGCCACTGGT AACAGGATTA GCAGAGCGAG GTATGTAGGC GGTGCTACAG	6840
GTGACCGTCG TCGGTGACCA TTGTCCTAAT CGTCTCGCTC CATACATCCG CCACGATGTC	6840
AGTTCTTGAA GTGGTGGCCT AACTACGGCT AACTAGAAG AACAGTATTT GGTATCTGCG	6900
TCAAGAACTT CACCACCGGA TTGATGCCGA TGTGATCTTC TTGTCATAAA CCATAGACGC	6900
CTCTGCTGAA GCCAGTTACC TTCGGAAAAA GAGTTGGTAG CTCTTGATCC GGCAAAACAA	6960
GAGACGACTT CGGTCAATGG AAGCCTTTTT CTCAACCATC GAGAACTAGG CCGTTTGTTT	6960
CCACCGCTGG TAGCGGTGGT TTTTTGTTT GCAAGCAGCA GATTACGCGC AGAAAAAAG	7020
GGTGGCGACC ATCGCCACCA AAAAAACAAA CGTTCGTCGT CTAATGCGCG TCTTTTTTTC	7020

FIG.13B-9

## pICAST OMN

GATCTCAAGA AGATCCTTTG ATCTTTTCTA CGGGGTCTGA CGCTCAGTGG AACGAAAAC	7080
CTAGAGTTCT TCTAGGAAAC TAGAAAAGAT GCCCCAGACT GCGAGTCACC TTGCTTTTGA	7080
CACGTTAAGG GATTTTGGTC ATGAGATTAT CAAAAGGAT CTTACCTAG ATCCTTTTGC	7140
GTGCAATTCC CTAAACCAG TACTCTAATA GTTTTCCTA GAAGTGGATC TAGGAAAACG	7140
GGCCGCAAT CAATCTAAAG TATATATGAG TAACTTGGT CTGACAGTTA CCAATGCTTA	7200
CCGGCGTTTA GTTAGATTTC ATATATACTC ATTTGAACCA GACTGTCAAT GGTACGAAT	7200
ATCAGTGAGG CACCTATCTC AGCGATCTGT CTATTTTCGTT CATCCATAGT TGCCTGACTC	7260
TAGTCACTCC GTGGATAGAG TCGCTAGACA GATAAAGCAA GTAGGTATCA ACGGACTGAG	7260
CCCGTCGTGT AGATAACTAC GATACGGGAG GGCTTACCAT CTGGCCCCAG TGCTGCAATG	7320
GGGCAGCACA TCTATTGATG CTATGCCCTC CCGAATGGTA GACCGGGGTC ACGACGTTAC	7320
ATACCGCGAG ACCCACGCTC ACCGGCTCCA GATTTATCAG CAATAAACCA GCCAGCCGGA	7380
TATGGCGCTC TGGGTGCGAG TGGCCGAGGT CTAAATAGTC GTTATTTGGT CGGTCGGCCT	7380
AGGGCCGAGC GCAGAAGTGG TCCTGCAACT TTATCCGCCT CCATCCAGTC TATTAATTGT	7440
TCCCGGCTCG CGTCTTCACC AGGACGTTGA AATAGGCGGA GGTAGGTCAG ATAATTAACA	7440
TGCCGGAAG CTAGAGTAAG TAGTTCGCCA GTTAATAGTT TGCGCAACGT TGTTGCCATT	7500
ACGGCCCTTC GATCTCATTC ATCAAGCGGT CAATTATCAA ACGCGTTGCA ACAACGGTAA	7500
GCTACAGGCA TCGTGGTGTC ACGCTCGTCG TTTGGTATGG CTTCAATCAG CTCCGGTTCC	7560
CGATGTCCGT AGCACCACAG TGCAGCAGC AAACCATACC GAAGTAAGTC GAGGCCAAGG	7560
CAACGATCAA GGCGAGTTAC ATGATCCCCC ATGTTGTGCA AAAAAGCGGT TAGCTCCTTC	7620
GTTGCTAGTT CCGCTCAATG TACTAGGGGG TACAACACGT TTTTCGCCA ATCGAGGAAG	7620
GGTCCTCCGA TCGTTGTCAG AAGTAAGTTG GCCGCAGTGT TATCACTCAT GGTTATGGCA	7680
CCAGGAGGCT AGCAACAGTC TTCATTCAAC CGGCGTCACA ATAGTGAGTA CCAATACCGT	7680
GCACTGCATA ATTCTCTTAC TGTCATGCCA TCCGTAAGAT GCTTTTCTGT GACTGGTGAG	7740
CGTGACGTAT TAAGAGAATG ACAGTACGGT AGGCATTCTA CGAAAAGACA CTGACCACTC	7740
TACTCAACCA AGTCATTCTG AGAATAGTGT ATGCGGCGAC CGAGTTGCTC TTGCCGGCG	7800
ATGAGTTGGT TCAGTAAGAC TCTTATCACA TACGCCGCTG GCTCAACGAG AACGGGCCG	7800

FIG.13B-10



## pICAST OMN

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TCAATACGGG ATAATACCGC GCCACATAGC AGAACTTTAA AAGTGCTCAT CATTGGAAAA	7860
AGTTATGCCC TATTATGGCG CGGTGTATCG TCTTGAAATT TTCACGAGTA GTAACCTTTT	7860
CGTTCTTCGG GGCAGAAACT CTCAAGGATC TTACCGCTGT TGAGATCCAG TTCGATGTAA	7920
GCAAGAAGCC CCGCTTTTGA GAGTTCCTAG AATGGCGACA ACTCTAGGTC AAGCTACATT	7920
CCCACTCGTG CACCCAACTG ATCTTCAGCA TCTTTTACTT TCACCAGCGT TTCTGGGTGA	7980
GGGTGAGCAC GTGGGTGAC TAGAAGTCGT AGAAAATGAA AGTGGTCGCA AAGACCCACT	7980
GCAAAAACAG GAAGGCAAAA TGCCGCAAAA AAGGGAATAA GGGCGACACG GAAATGTTGA	8040
CGTTTTTGTC CTTCCGTTTT ACGGCGTTTT TTCCCTTATT CCCGCTGTGC CTTTACAACT	8040
ATACTCATAC TCTTCCTTTT TCAATATTAT TGAAGCATTT ATCAGGGTTA TTGTCTCATG	8100
TATGAGTATG AGAAGGAAAA AGTTATAATA ACTTCGTAAA TAGTCCCAAT AACAGAGTAC	8100
AGCGGATACA TATTTGAATG TATTTAGAAA AATAAACAAA TAGGGGTTCC GCGCACATTT	8160
TCGCCTATGT ATAACTTAC ATAAATCTTT TTATTTGTTT ATCCCCAAGG CGCGTGTAAG	8160
C	8161
G	8161

FIG.13B-11

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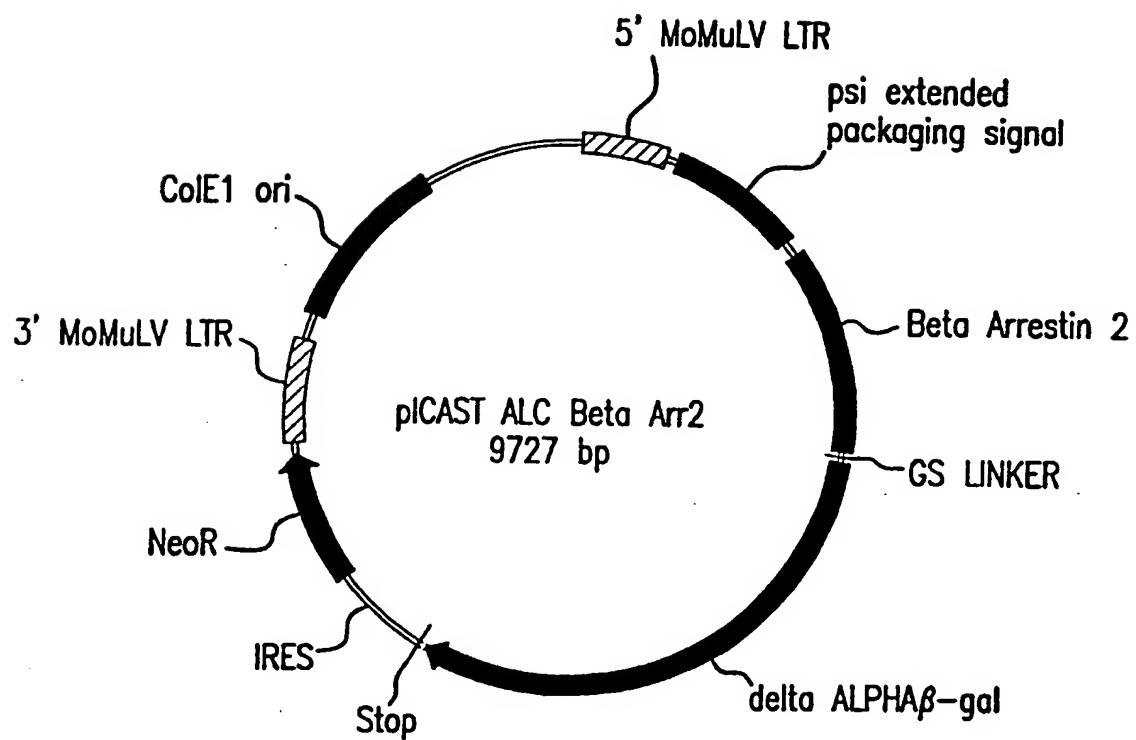


FIG.14

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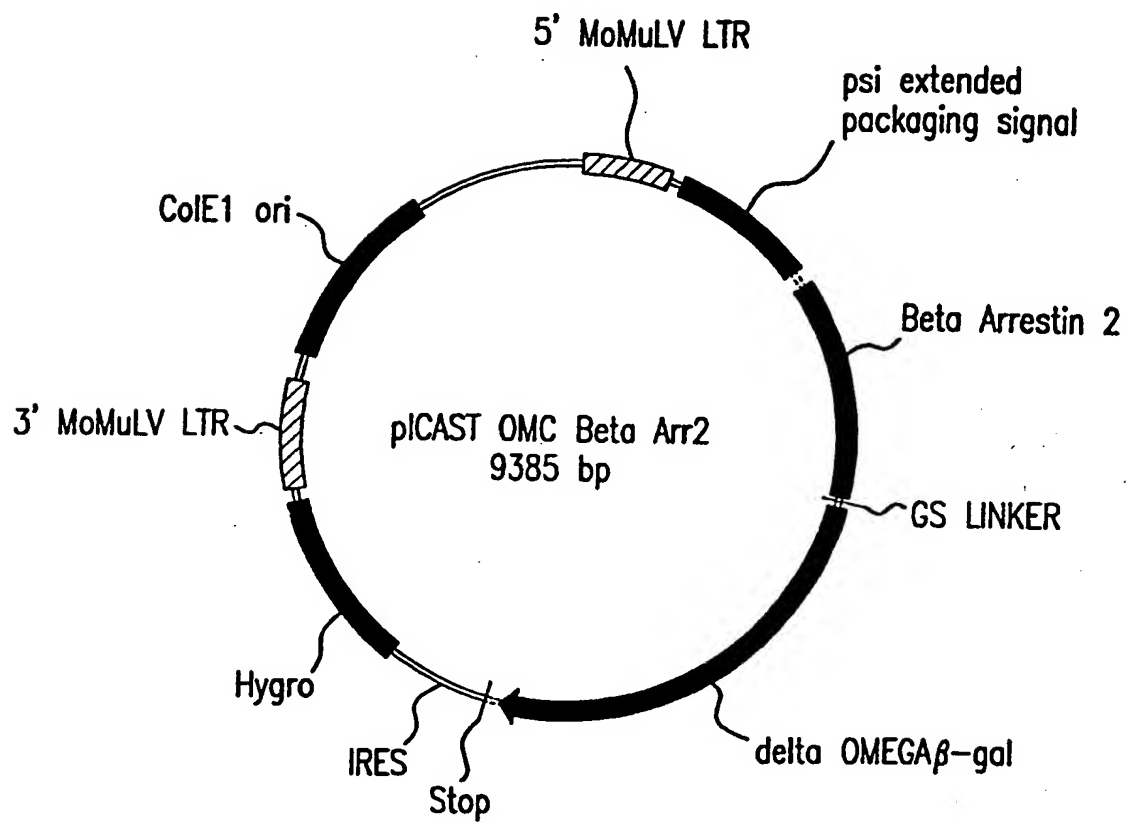


FIG.15

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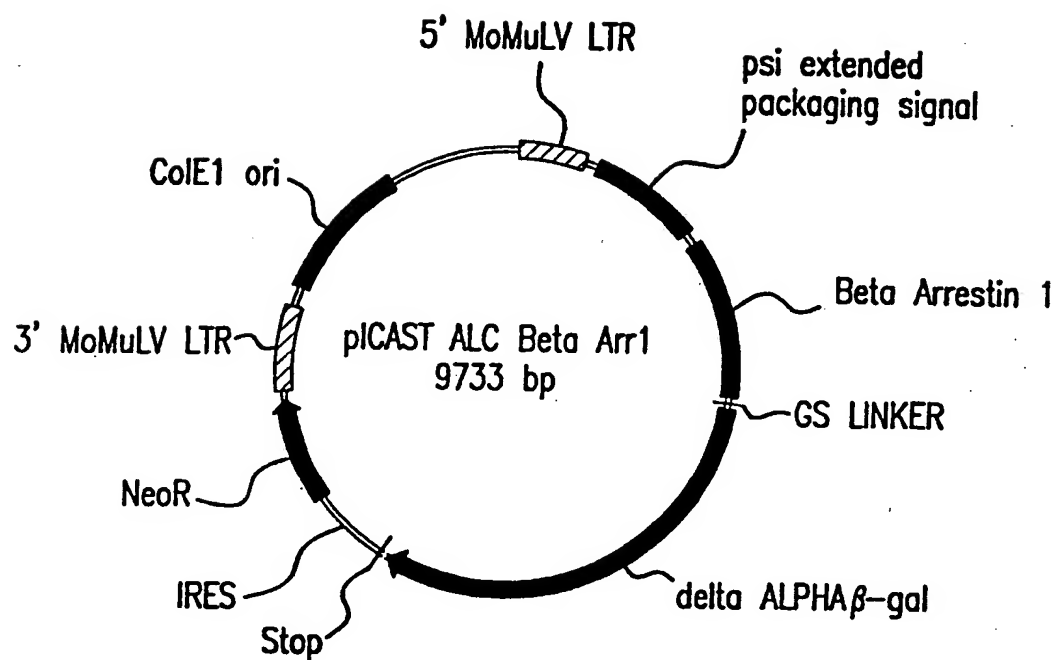


FIG.16

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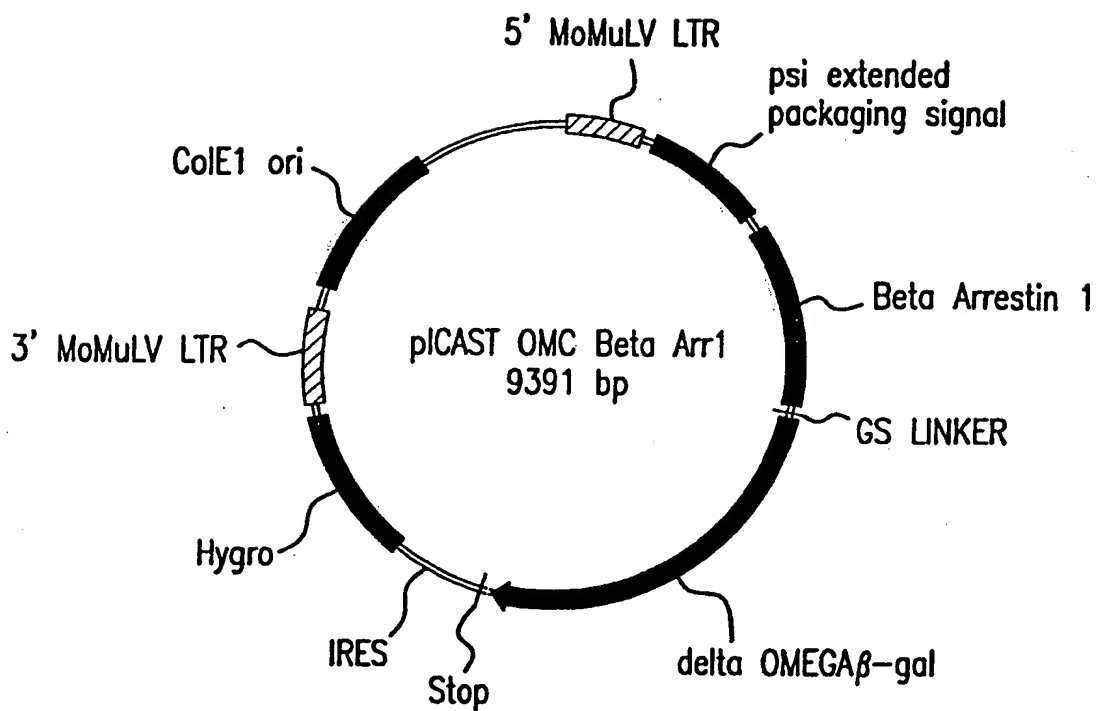


FIG.17

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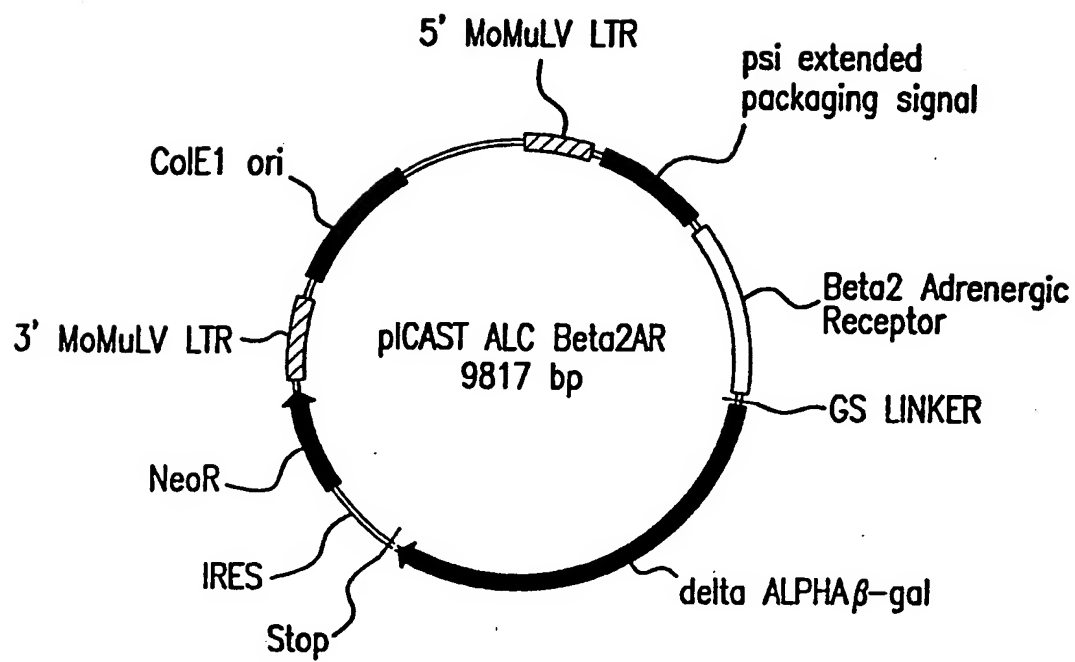


FIG.18

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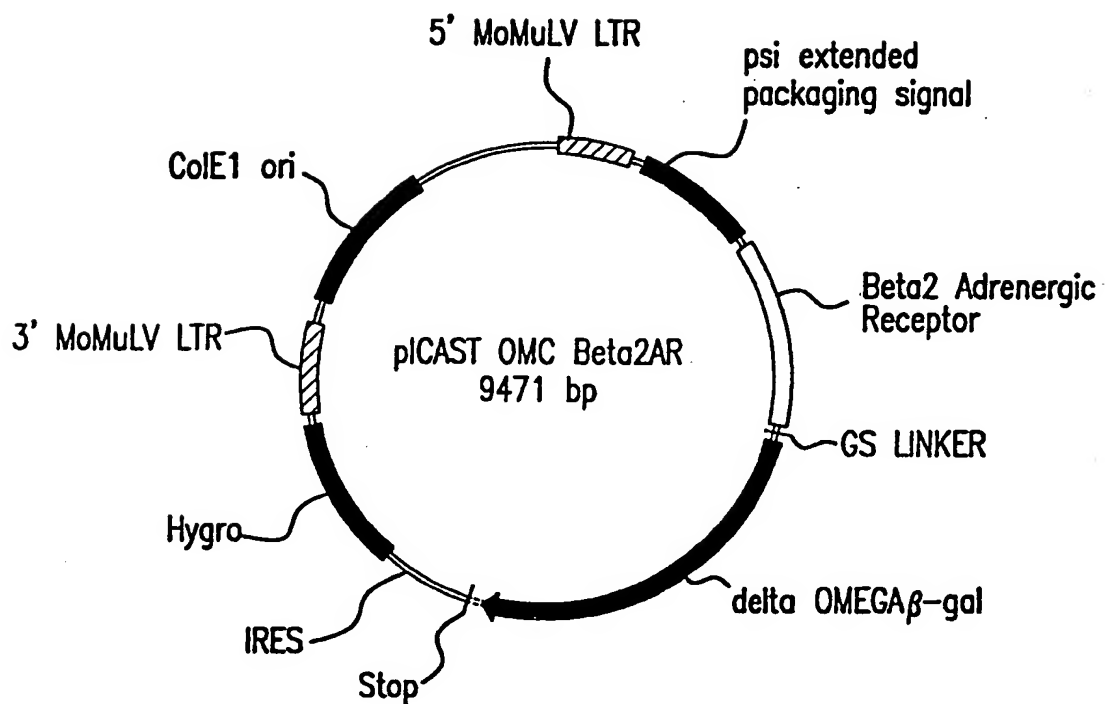


FIG.19

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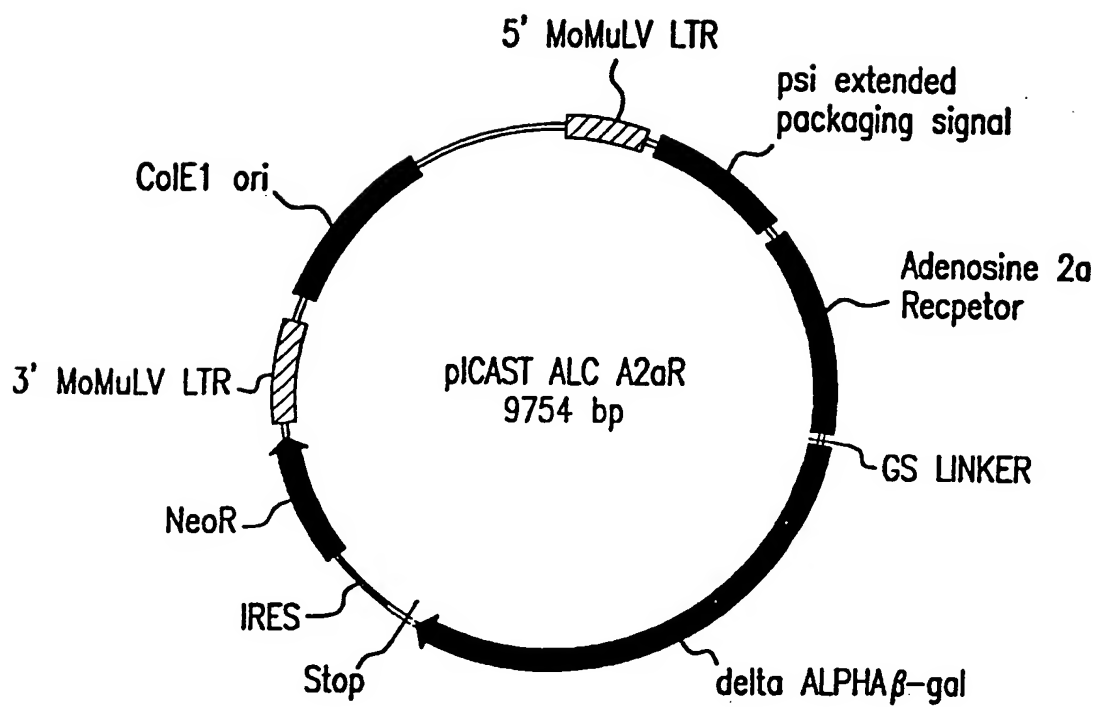


FIG.20



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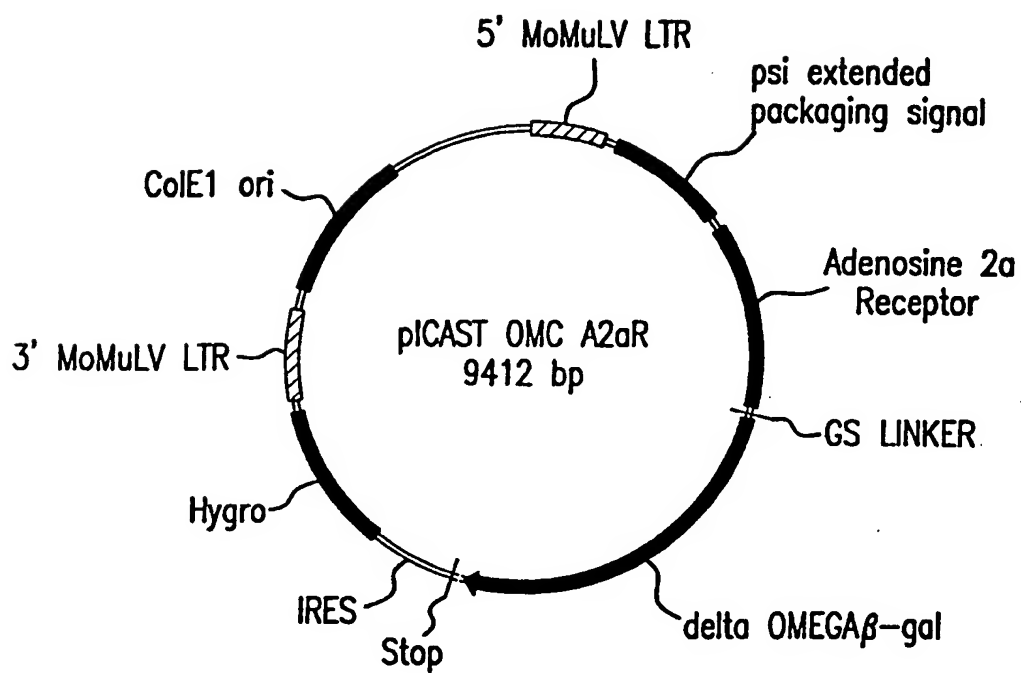


FIG.21

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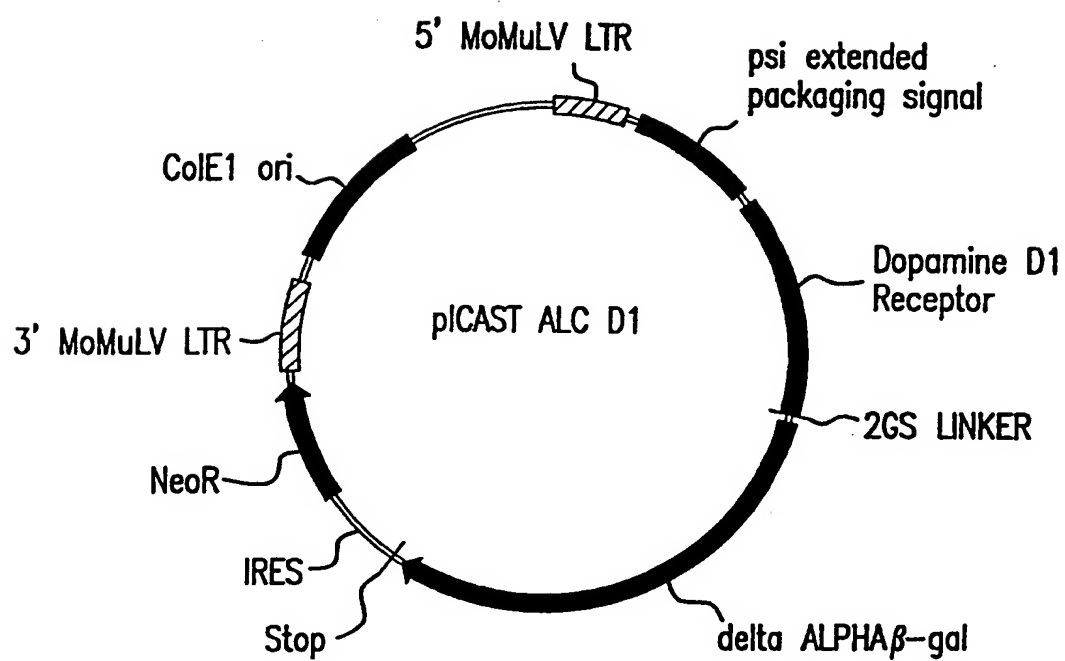
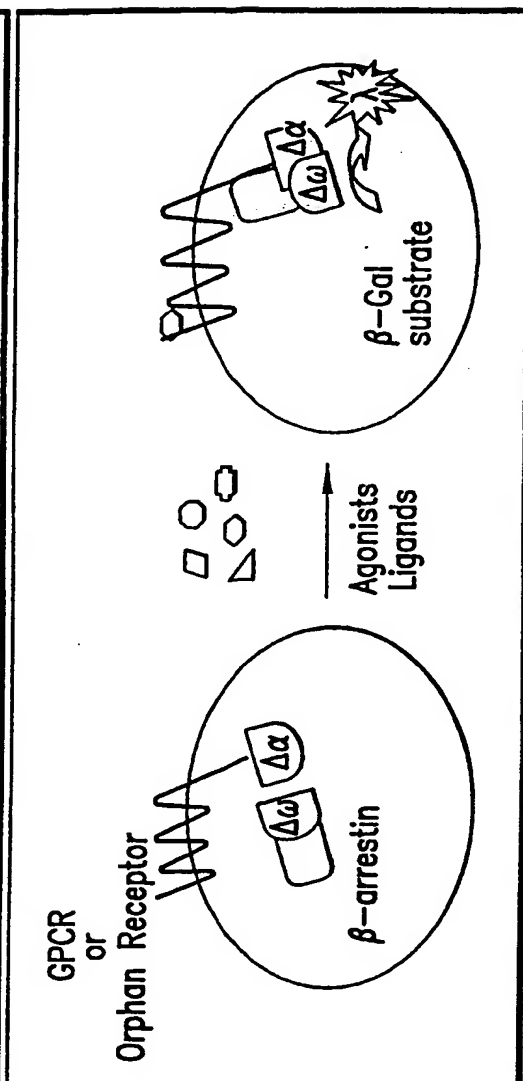


FIG.22

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Functional GPCR Activation Assay and Ligand Fishing for Orphan Receptors  
by  $\beta$ -galactosidase mutant complementation in ICAS<sup>TM</sup> System



Examples

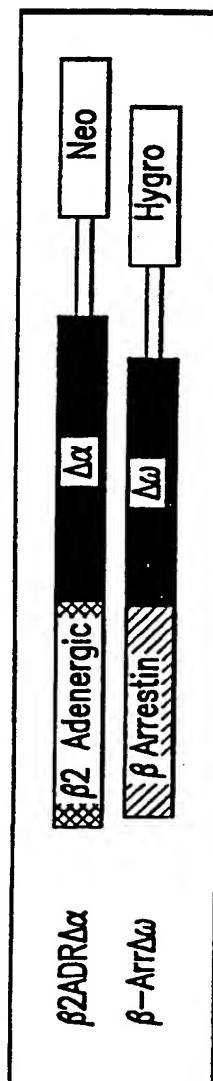


FIG. 23

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/24043

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : G01N 33/52; C07H 21/04; C07K 14/00; C12N 15/12

US CL : 435/7.1, 7.2, 69.7; 436/501; 530/350; 536/23.4

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.1, 7.2, 69.7; 436/501; 530/350; 536/23.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: MEDLINE, USPATFULL

search terms: fusion#, hybrid#, chimcr?, arrestin#, beta galactosidase#, protein-protein interaction

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,891,646 A (BARAK et al.) 06 April 1999, see entire document.	1-30
Y	BARAK et al. A beta-Arrestin/Green Fluorescent Protein Biosensor for Detecting G Protein-coupled Receptor Activation. The Journal of Biological Chemistry. 31 October 1997, Vol. 272, No. 44, pages 27497-27500, see entire document.	1-30
Y	ROSSI et al. Monitoring Protein-protein Interaction in Intact Eukaryotic Cells by beta-Galactosidase Complementation. Proceedings of the National Academy of Science. August 1997, Vol. 94, pages 8405-8410, see entire document.	1-30



Further documents are listed in the continuation of Box C.



See patent family annex.

•

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document defining the general state of the art which is not considered to be of particular relevance

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document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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earlier document published on or after the international filing date

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document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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document referring to an oral disclosure, use, exhibition or other means

\*O\*

document published prior to the international filing date but later than the priority date claimed

\*A\*

document member of the same patent family

Date of the actual completion of the international search

15 NOVEMBER 2000

Date of mailing of the international search report

05 DEC 2000

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Box PCT  
Washington, D.C. 20231

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